A CHEMOENZYMATIC AND INTRAMOLECULAR DIELS-ALDER APPROACH TOWARD THE SYNTHESIS OF MORPHINAN SKELETONS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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By

Bennett H. Novak

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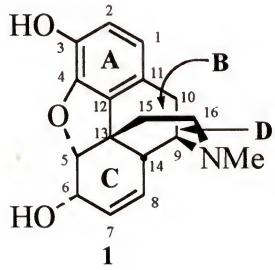
Chairman: Tomas Hudlicky
Major Department: Chemistry

A model study designed to determine the stereochemistry of intramolecular Diels-Alder adducts derived from dienes of (*E,Z*)-geometry is described. The synthesis of the Diels-Alder precursors from the biooxidation products of substituted aromatics as well as the application to the construction of the morphinan skeleton is also described. It was determined that the (*E,Z*)-geometry of the diene did not allow the intramolecular Diels-Alder cycloaddition to take place resulting in elimination of the ether linkage.

CHAPTER 1
INTRODUCTION

For well over one hundred years, morphine (**1**) has been known to humankind for its analgesic and euphoric properties. It was not until the early 1900s that the



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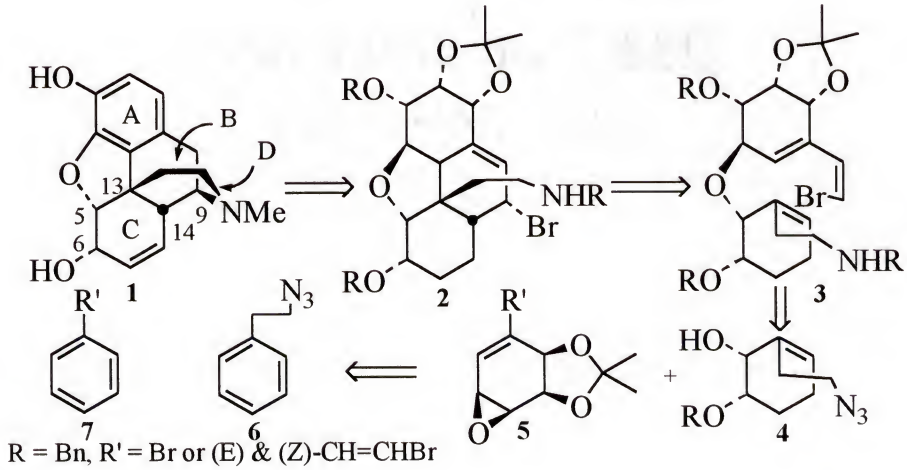
structure of morphine was deduced and the early 1950s that the first published synthesis appeared. Yet morphine has attracted the interest of synthetic chemists for years. It is a relatively small alkaloid consisting of three carbocyclic and two heterocyclic rings. It also consists of five contiguous stereocenters, one of which is benzylic and quaternary. Chemists have sought a method by which to construct this alkaloid in a short and economical method. Currently, none of the published syntheses can compete with the current method of morphine isolation-extraction of the unripened seed of the opium poppy, *Papaver somniferum*. Morphine and its derivatives are still widely used in the field of medicine. If the supply of the world's opium poppy seed were ever in jeopardy, a cheap and concise synthesis would be required.

There are only two syntheses of morphine that report the use of the Diels-Alder reaction and neither one uses the reaction as a focal step but instead use it to help construct the phenanthrene core of morphine. There have been several published approaches to morphine via the intramolecular Diels-Alder (IMDA) reaction but none have yet resulted in a complete formal synthesis.

This thesis describes the use of a combined enzymatic dihydroxylation and IMDA strategy to construct the morphinan skeleton. The enzymatic dihydroxylation sets the C5 and C6 stereocenters of the morphine skeleton while the IMDA reaction constructs the B- and O-rings of the skeleton while also setting the C9, C12, and C13 stereocenters.

Based on previous model studies using an IMDA reaction performed in the Hudlicky laboratories, a 3rd generation approach was designed. Scheme 1 shows the projected outline of the synthesis.

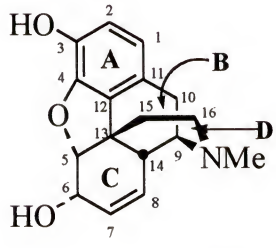


Scheme 1

CHAPTER 2
HISTORICAL

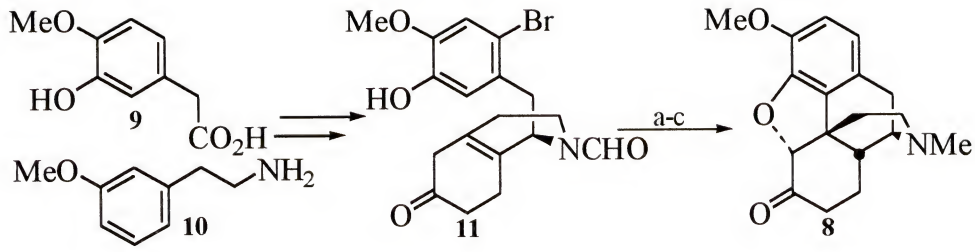
A Brief Overview of Morphine and Morphine Syntheses

Morphine (**1**), long known for its analgesic and euphoric properties, was first isolated in 1803 by Derosne.[1] In 1806, the description of the isolation of morphine was reported to the Institute of France by Sequin.[2] Serturner[3] was credited with the first isolation of morphine later that same year. Over 100 years later, Robinson[4,5] published



(-)-Morphine (**1**)

the first proposed structure of morphine. This was later confirmed, approximately 25 years later, in 1952 by the first synthesis of morphine published by Gates.[6] Since this initial synthesis over 20 total or formal total syntheses of morphine have been published.[7] This relatively small alkaloid, isolated from the unripened seed of the opium poppy of *Papaver sonmiferum*, provides a very complex synthetic target. Among the three carbocyclic and two heterocyclic rings there are five contiguous



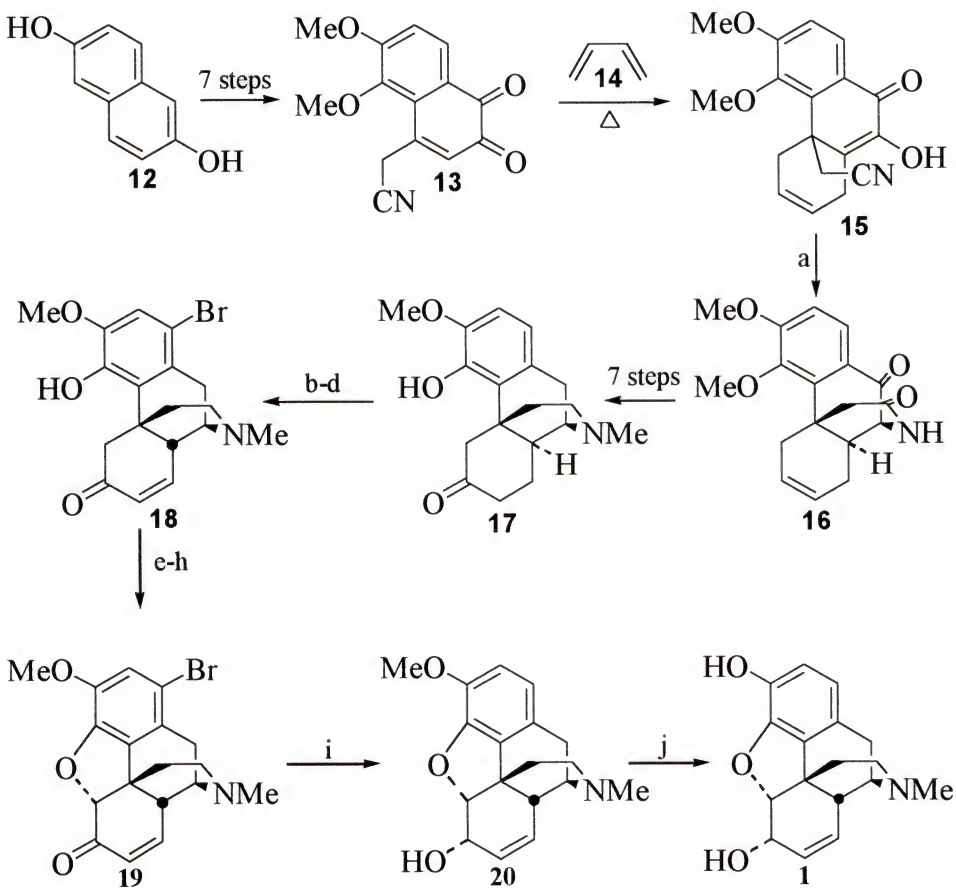
Conditions: a) 14% NH_4F HF, CF_3SO_3H, 0 °C; b) 10:1 MeOH, aq. HCl; c) i. Br_2, AcOH; ii. 1 N NaOH; iii. H_2, Pd/C, AcOH, HCHO, NaOAc.

Scheme 2

stereocenters, one of which is benzylic and quaternary. It is still a challenge for synthetic chemists to design a short, economical synthesis of this compound. Rice's synthesis, reported in 1980,[8] is considered the most practical, requiring only 9 steps to dihydrocodienone (**8**) (Scheme 2) from compounds **9** and **10** and proceeding in an overall yield of 29%. Suprisingly, of all the reported syntheses only two researchers. Gates[6] and Tius[9] utilized a Diels-Alder reaction to construct the ABC ring system or phenanthrene core of morphine. This historical will briefly outline the morphine syntheses published to date. The general aspects of the inter- and intramolecular Diels-Alder reaction will also be discussed as well as approaches to the morphinan skeleton using the intramolecular Diels-Alder reaction.

Gates's initial synthesis[6] started with the conversion of naphthalene diol **12** to the diketone **13** (Scheme 3). An intermolecular Diels-Alder reaction with 1,4-butadiene **14** afforded the ABC ring system of morphine, **15**. The D-ring was closed via a catalytic hydrogenation in the presence of copper chromite to give the lactam **16**, although the stereochemistry at C14 was incorrect The racemic mixture of **16** was resolved by forming the dibenzoyltartaric acids. This material was converted into β-14-

dihydrothebainone **17**, which is one of the most commonly intercepted intermediates in other formal syntheses. The stereochemistry at C14 was inverted through bromination followed by conversion to enone **18**. In order to close the dihydrofuryl ring, the enone was reduced and the resulting ketone was treated with two equivalents of bromine



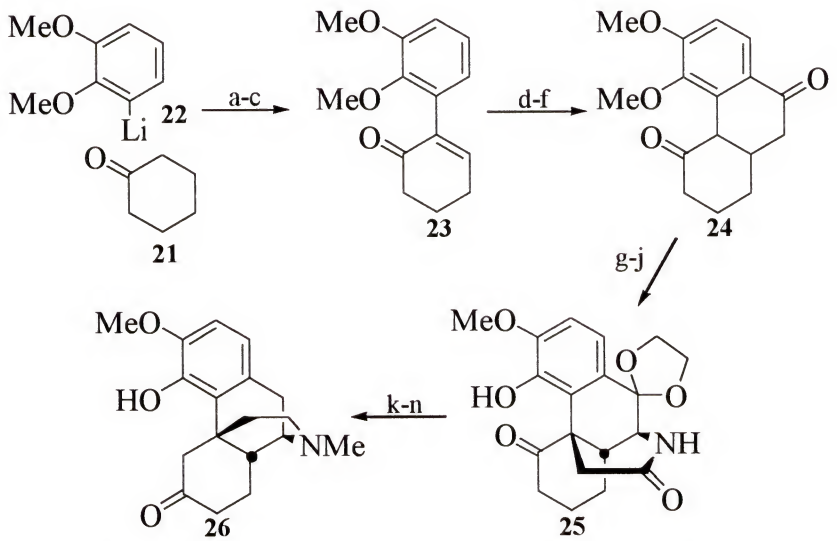
Conditions: a) H_2, $CuCrO_3$; b) Br_2; c) 2,4-DNPH; d) HCl, acetone; e) H_2, PtO_2; f) Br_2; g) 2,4-DNPH; h) HCl, acetone; i) $LiAlH_4$, j) py-HCl, 220 °C.

Scheme 3

followed by hydrazone formation to afford **19**. Lithium aluminum hydride was then used to remove the aryl bromide as well as to reduce stereospecifically the ketone to

give the alcohol with the correct stereochemistry resulting in codeine (**20**), which was converted in one step to (-)-morphine (**1**).

A few years later, Ginsburg completed the second synthesis of morphine by intercepting dihydrothebainone to formalize his synthesis.[10] Starting from the condensation of cyclohexanone **21** and *ortho*-lithiated veratrole **22** followed by elimination and allylic oxidation, enone **23** was produced (Scheme 4). A Michael addition with dibenzyl malonate, decarboxylation and Friedel-Crafts annulation

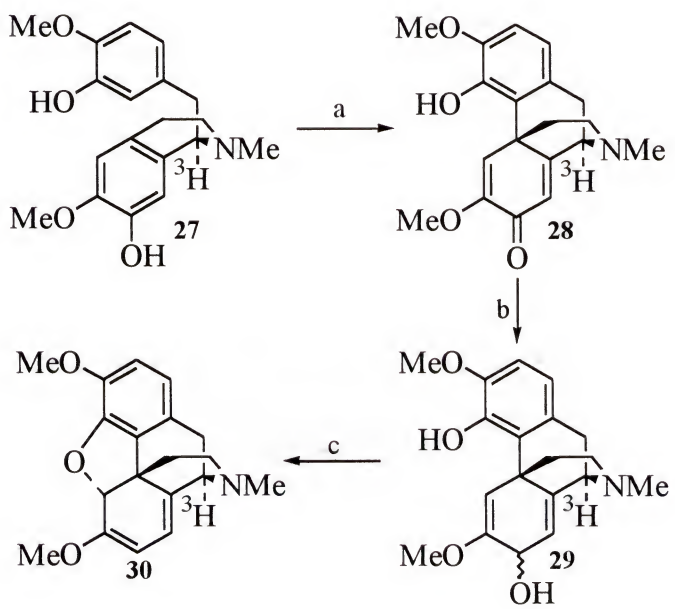


Conditions: a) HO_2CCO_2H, PhMe, heat; b) NOCl; c) i. pyr, heat; ii. aq. H_2SO_4, heat; d) dibenzyl malonate, KO^tBu; e) i. H_2, Pd; ii. heat; f) HF; g) ethylene glycol, *p*-TsOH, heat; h) i. AmONO, NaOEt; ii. H_2, Pd, HCl; i) acetoxyacetyl chloride, 2 eq. pyr., $CHCl_3$; j)ethylene glycol, heat; k) i. AmONO, NaOAc; ii. aq. acid; l) NH_2NH_2, ethylene glycol, heat; m) i. aq. acid; ii. $LiAlH_4$; n) i. CH_2O, HCO_2H, heat; ii. Ph_2CO, KO^tBu; iii. resolution.

Scheme 4

afforded the phenanthrene core of morphine **24**. The amino group was introduced at C9 through a selective protection-deprotection strategy. The formation of the D-ring occurred spontaneously, with the correct C13 stereochemistry, while selective deprotection of the C4 methyl ester occurred to give **25**. Finally, the ketone functionality at C6 was introduced and the undesired carbonyls at C5 and C10 were removed. Reduction of the lactam, N-methylation, oxidation, and resolution afforded dihydrothebainone **26**.

Barton published a biomimetic synthesis of thebaine in 1963,[11] thus formalizing another synthesis of morphine (Scheme 5). He used a manganese dioxide coupling of radiolabelled reticuline **27** to form radioactive salutaridine **28**, a 0.012% conversion according to a radioisotope dilution study. The salutaridine **28** was reduced to a

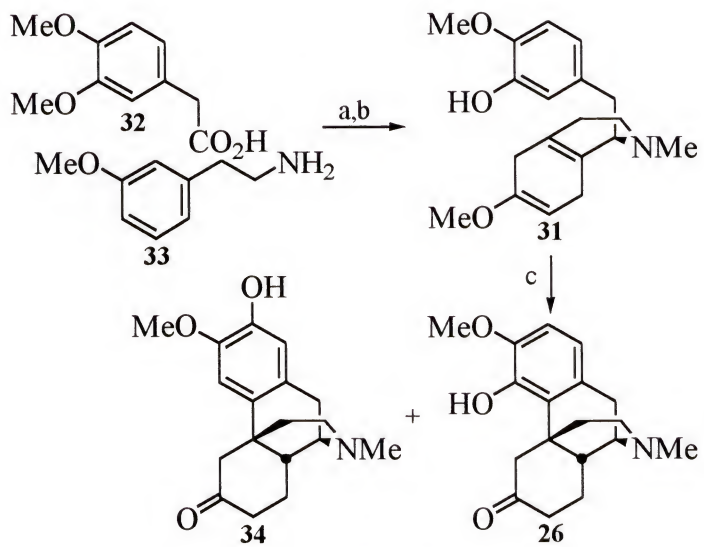


Conditions: a) MnO_2; b) $NaBH_4$; c) < pH 4, room temperature.

Scheme 5

mixture of epimeric diols, **29** which underwent an acid catalyzed allylic displacement to give thebaine **30**.

Two groups - Grewe and coworkers[12] and Morrison along with Waite and Shavel[13] - published simultaneous accounts of the synthesis of dihydrothebainone **26** via an acid catalyzed coupling of the benzyl tetrahydroisoquinoline derivative **31**



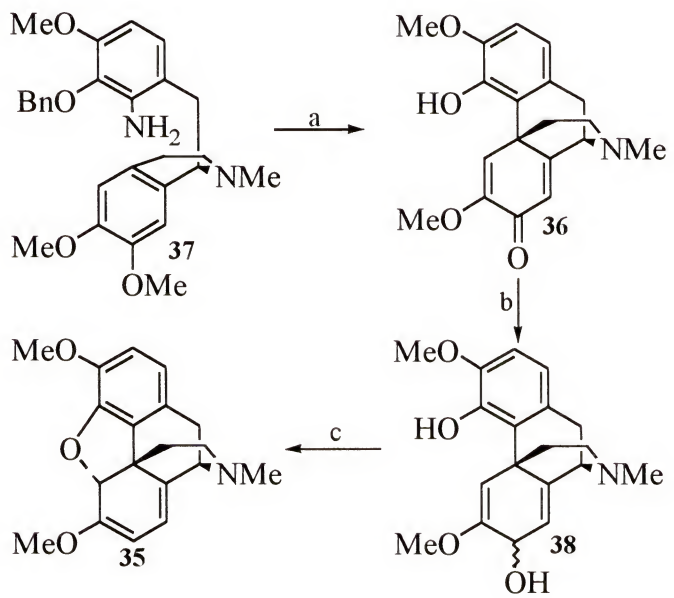
Conditions: a) i. amidation; ii. Bischler-Napieralski; iii. reduction; methylation; b) $Na/^tBuOH/NH_3$; c) 10% aq. HCl.

Scheme 6

(Scheme 6). Compound **31** was synthesized starting with the amidation of **32** and **33** followed by a Bischler-Napieralski reaction, reduction, N-methylation and Birch reduction. Morrison, Waite and Shavel used a refluxing 10% HCl solution to form the desired *ortho* coupled product **26** in 3% yield. The *para*-product **34** was formed in 37%

yield. Grewe used phosphoric acid to perform the cyclization obtaining similar yields. Many other groups utilized modified "Grewe" cyclizations to enhance the *ortho* selectivity.

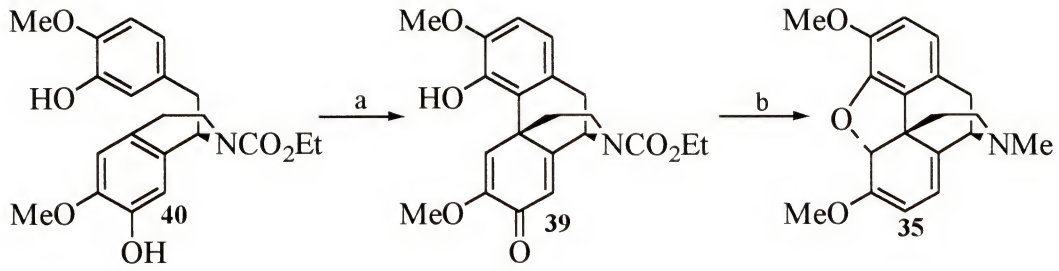
In 1969, Kametani and coworkers[14] used a Pschorr-type cyclization to produce thebaine, **35** (Scheme 7). Racemic salutaridine **36** was produced from the thermal



Conditions: a) i. $NaNO_2$, H_2SO_4, AcOH; ii. 70 °C; b) $NaBH_4$; c) 1 M HCl.
Scheme 7

decomposition of the diazonium salt of **37** in a yield of 1.1%. Thebaine **35** was produced via Barton's method of reduction to the epimeric diols, **38**, followed by acid-catalyzed allylic displacement using the phenolic group to give **35**.

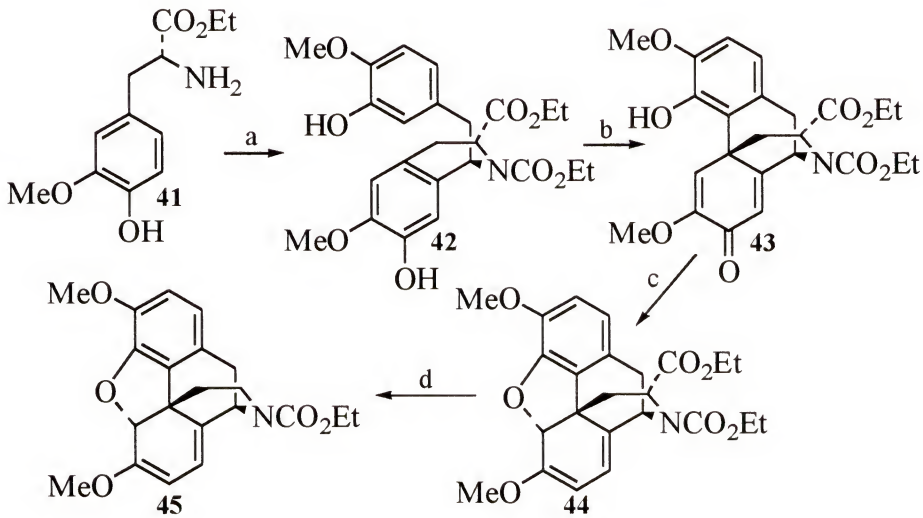
Schwartz also published a synthesis of racemic thebaine based on the Grewe-type cyclization.[15a] In this case thallium tristrifluoroacetate was used to give the



Conditions: a) $Tl(TFA)_3$, CH_2Cl_2, -78 to -20 °C; b) i. $LiAlH_4$; ii. 1 M HCl.

Scheme 8

salutaridine derivative **39** in 23% yield (Scheme 8). The synthesis of morphine was

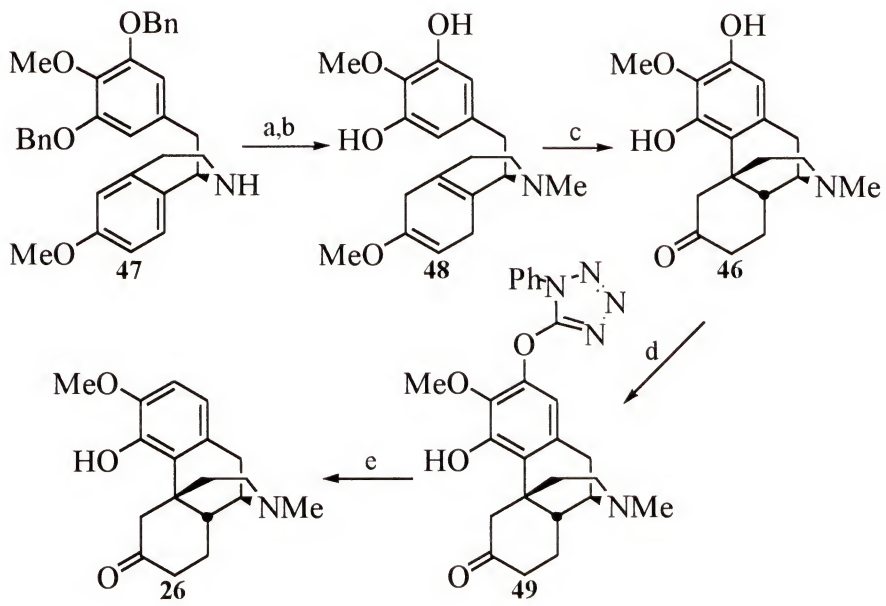


Conditions: a) i. 3-benzyloxy-4-methoxyphenyl acetic acid, 1,1-carbonyldiimidazole, THF; ii. H_2, Pd/C, EtOAc; iii. MeO_2CCl, CH_2Cl_2, Et_3N; iv. $POCl_3$, MeCN; v. $NaBH_4$, MeOH; vi. MeO_2CCl, Na_2CO_3, MeOH; vii. Na_2CO_3, H_2O; b) $PhI(OAc)_2$, TFA; c) i. $NaBH_4$; ii. N,N-DMF dineopentenyl acetal; d) Barton decarboylation.

Scheme 9

formalized using Barton's reduction and acid treatment to afford thebaine **35**. Several years later, in 1988, Schwartz published an enantioselective synthesis using the amino acid derivative **41** (Scheme 9).[15b] Compound **41** was condensed with 3-benzyloxy-4-methoxyphenyl acetic acid in a manner similar to Grewe[12] and Morrison and Waite and Shavel[13] to afford **42**. The coupling was performed using iodosobenzene diacetate to give to salutaridine **43**. Reduction followed by ring closure afforded **44**, and Barton decarboxylation gave the known thebaine derivative **45**.

Beyerman also used the Grewe-type cyclization to form the dihydrothebainone derivative **46**, but to overcome the *ortho-para* selectivity he used a symmetrical arene.[16]

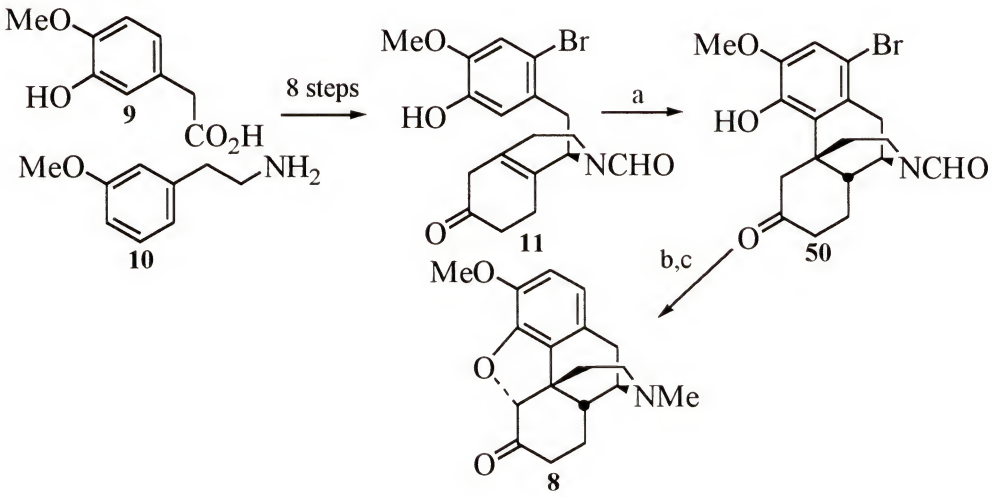


Conditions: a) CH_2O, H_2, Pt/C; b) Li/NH_3, ^tBuOH; c) HCl, Et_2O; d) 5-chloro-1-phenyltetrazole, K_2CO_3, DMF, 70 °C; e) H_2, Pd/C, 50-55 °C.

Scheme 10

Birch reduction of **47** afforded **48** which underwent the Grewe-type cyclization using HCl in ether (Scheme 10). The extra phenolic group was removed selectively by forming the tetrazole derivative **49** then removing it under hydrogenolysis conditions to give (-)-dihydrothebainone **26**, thus formalizing his synthesis.

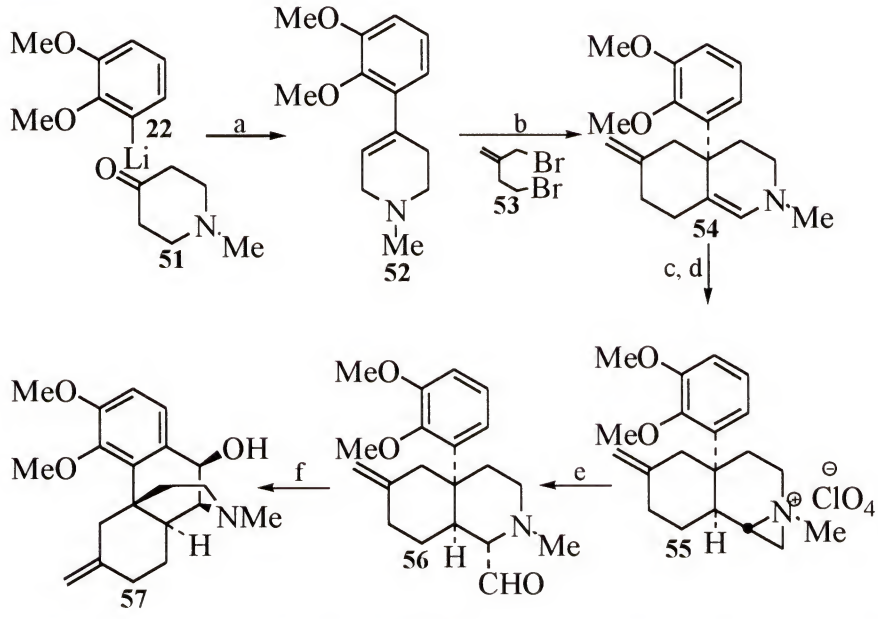
As mentioned earlier, Rice's total synthesis is credited as the most practical



Conditions: a) 14% NH_4F HF, CF_3SO_3H, 0 °C; b) 10:1 MeOH, aq. HCl; c) i. Br_2, AcOH; ii. 1 N NaOH; iii. H_2, Pd/C, AcOH, HCHO, NaOAc.
Scheme 11

synthesis to date.[8] Starting with compounds similar to those of Grewe[12] and using a strategy similar to Beyerman's,[16] a bromine atom was used to block the formation of the undesired *para* coupled product (Scheme 11). The ketone **11** underwent coupling under acidic conditions to give bromonordihydrothebaine **50** in a 60% yield which was then converted to codeine **8** in a few more steps.

Evans's synthesis[17] starts similarly to Ginsburg's[10] with the *ortho*-lithiated veratrole **22** undergoing coupling to piperidone **51** to give **52** after dehydration (Scheme 12). Formation of the enamine and selective coupling with the allylic terminus of the



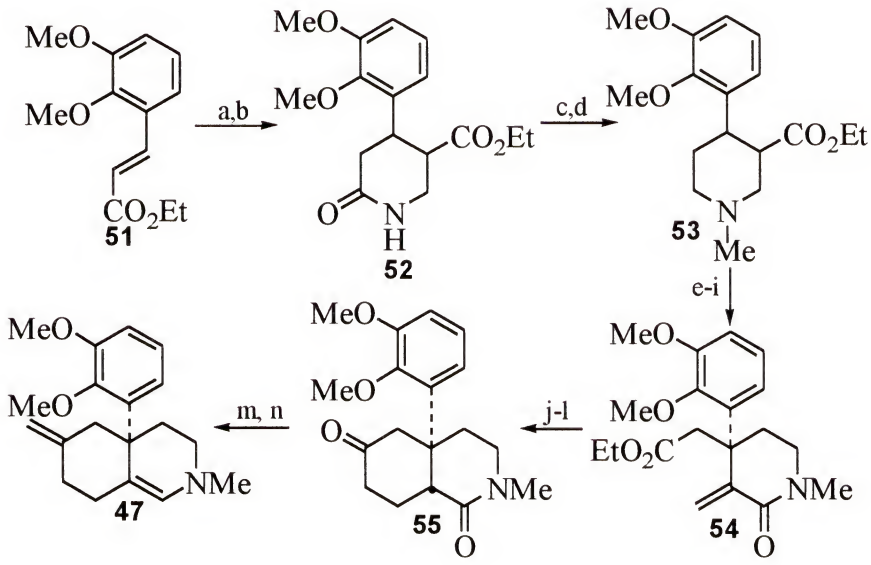
Conditions: a) i. Et_2O, 0 °C.; *p*-TsOH, PhMe, heat; b) i. nBuLi, THF, -10 °C, **53**; ii. NaI, K_2CO_3, MeCN, heat; c) $HClO_4$, Et_2O, MeOH, 50 °C; d) CH_2N_2, CH_2Cl_2; e) DMSO; f) BF_3-Et_2O, PhMe, -10 °C.

Scheme 12

dibromide, **53**, followed by intramolecular enamine alkylation gave **54**. Perchloric acid formed the *cis*-fused ring junction and treatment with diazomethane afforded the aziridinium salt **55**. The three-membered ring was opened in DMSO and further oxidized to give aldehyde **56**. The B-ring was formed in the presence of boron trifluoride etherate to give the ABCD ring system of morphine **57**. Evans then intercepted Gates' intermediate *epi*-14-dihydrothebainone (**17**) to formalize his synthesis through a sequence of methanesulfonation and reduction of the mesylate with

$LiBEt_3H$ to remove the hydroxy group followed by Lemieux-Johnson oxidation (OsO_4, $NaIO_4$) under acid conditions.

Rapoport constructed cinnamate **58** in two steps from *o*-vanillin (Scheme 13).[18] A Michael addition with ethyl cyanoacetate followed by a reduction and lactam cyclization led to the lactam **59**. Amide reduction and N-methylation afforded **60**. Nipecotate **60** underwent a benzylic oxidation followed by an orthoester Caisen rearrangement and acid catalyzed hydrolysis to acid **61**. Homologation to the β-keto

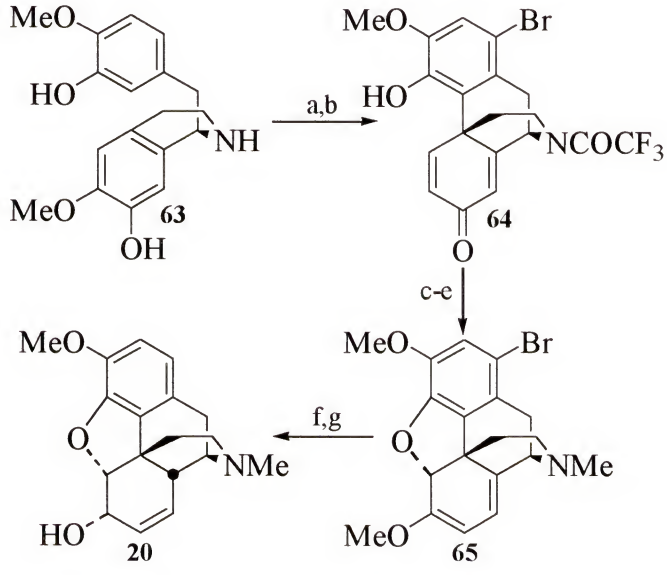


Conditions: a) EtO_2CCH_2CN, NaOEt, EtOH, heat; b) i. H_2, Pt, EtOH; ii. PhMe, heat; c) i. Me_3OBF_4, CH_2Cl_2; ii. $NaBH_4$, EtOH; d) CH_2O, H_2, Pd/C, EtOH; e) i. NaOH, H_2O, MeOH, reflux; ii. AcOH; iii. Ac_2O; f) SeO_2, PhCl, 100 °C; g) HCO_2H; h) K_2CO_3, MeOH; i) i. $CH_3C(OMe)_3$; ii. hydrolysis; j) i. $(imid)_2CO$, CH_2Cl_2; ii. $^tBuO_2CCH_2CO_2{}^tBu$, isopropylmagnesium bromide; k) NaOMe, MeOH; l) TFA, CH_2Cl_2; m) CH_2PPh_3, THF; n) DIBAL, THF, 0 °C.

Scheme 13

ester, intramolecular Michael addition and decarboxylation afforded ketone **62**. Ketone **62** was then converted in two steps to Evan's enamine intermediate **54**, thereby formalizing his synthesis.

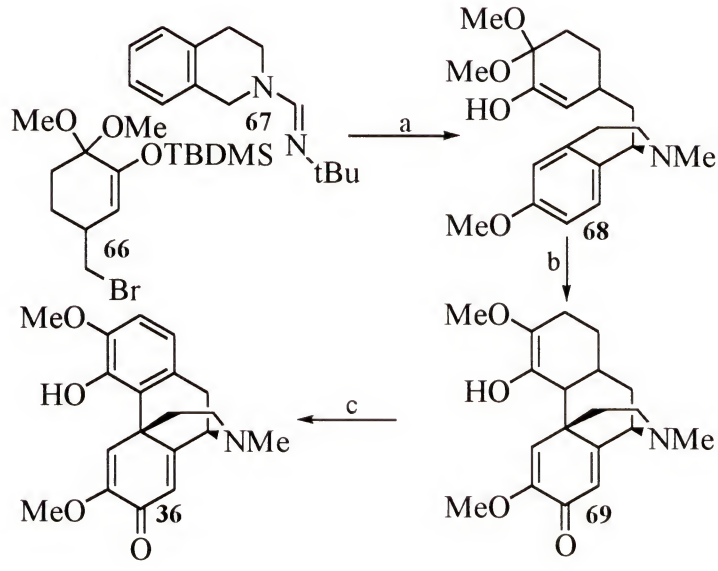
In White's morphine synthesis,[19] the B-ring was closed by means of an aryliodoso complex after a protection and bromination sequence of (-)-norreticuline **63** to form the salutaridine derivative **64** in yields around 10% (Scheme 14). Hydrolysis followed by N-methylation, reduction, and mild dehydration led to **65**. The thebaine derivative **65** underwent hydrolysis, migration of the double bond into conjugation and treatment with lithium aluminum hydride to remove the bromide and reduce the enone to form (-)-codeine **20**.



Conditions: a) i. Br_2, AcOH, ii. TFAA, pyr; b) $PhI(TFA)_2$, CH_2Cl_2, -40 °C; c) K_2CO_3, $MeOH_{(aq.)}$; d) CH_2O, $NaBH_4$; e) N,N-DMF, neopental acetal; f) i. $Hg(OAc)_2$, HCO_2H, H_2O; ii. HCl then H_2O; g) $LiAlH_4$.

Scheme 14

To combat the problems of *ortho-para* selectivity, Schafer used a nonaromatic A ring moeity **66** (Scheme 15).[20] This was coupled via an α-lithiation of formamidine **67**,

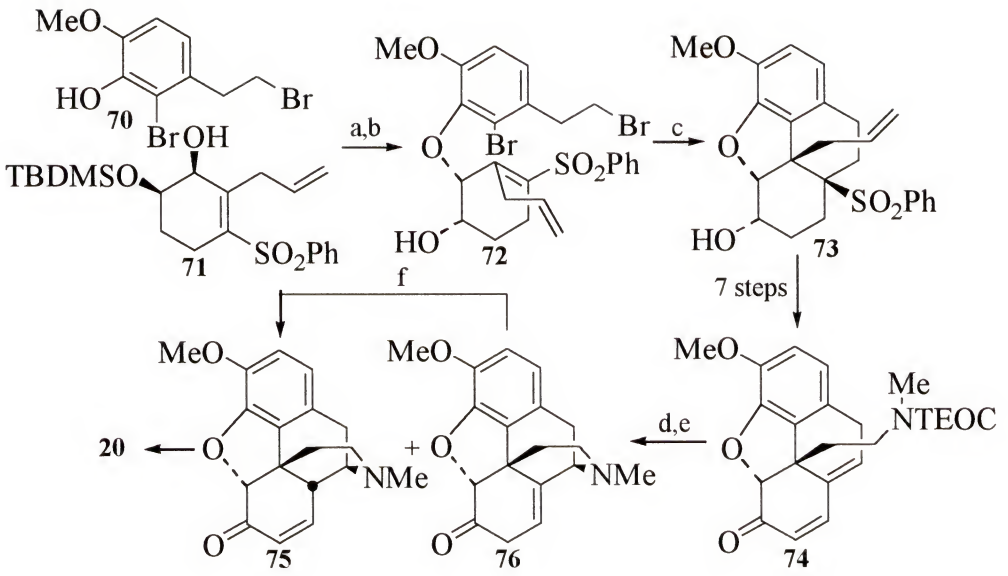


Conditions: a) i. LDA, -78 C; ii. $NaBH_4$, MeOH; b) 1.5 eq. $SnCl_4$, CH_2Cl_2; c) DDQ, PhMe.

Scheme 15

alkylation and reductive cleavage to afford **68**. Compound **68** underwent cyclization with 1.5 equivalents of tin tetrachloride to afford compound **69** which was oxidized in the presence of DDQ to give salutaridine **36**.

Fuchs' morphine synthesis used a tandem coupling reaction to construct the B ring of the morphine skeleton (Scheme 16).[21] Under Mitsunobu conditions, he coupled phenol **70** with alcohol **71**, then performed a TBDMS deprotection, followed by oxidation and reduction to give **72** with the correct stereochemistry at C5 and C4. A metal halogen exchange with n-butyl lithium resulted in an intramolecular conjugate



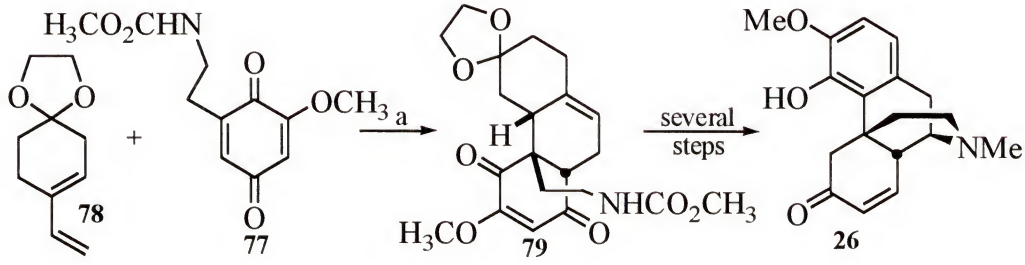
Conditions: a) Bu_3P, DEAD, THF; b) i. 48% HF, MeCN; ii. CrO_3, H_2SO_4, aq. acetone, 0 °C; iii. DIBAL, THF, -78 °C; c) nBuLi, THF, -78 °C; d) TFA; e) $CHCl_3$, $NaHCO_{3(aq.)}$; f) HCl, Et_2O then 0.2 M HaOH.

Scheme 16

addition to form the C12-C13 bond followed by an alkylation to close the B-ring at C14 to afford **73**. Through a sequence of several steps the nitrogen functionality was introduced giving compound **74** which was treated with TFA, then aqueous sodium bicarbonate to give a mixture of codeinone **75** and neopinone **76**. The double bond of neopinone **76** was isomerized to give codeinone **75** and reduction with sodium borohydride led to codeine **20**.

Forty years after Gates's initial synthesis of morphine,[6] Tius published the only other morphine synthesis which uses a intermolecular Diels-Alder reaction (Scheme 17).[9] Quinone **77** and diene **78** underwent a Diels-Alder cycloaddition to afford the adduct **79** in 86% yield. Through several more steps he was able to aromatize the A-

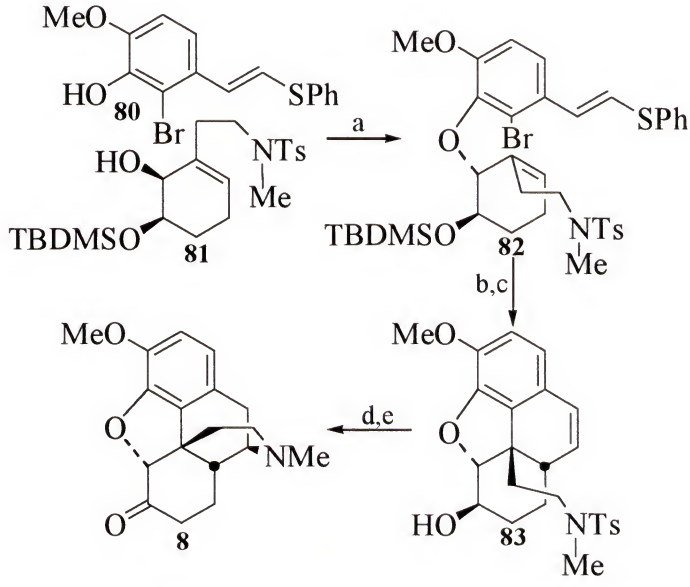
ring and form the D-ring to intercept Gates' thebainone intermediate **26**,[6] thus formalizing his synthesis.



Conditions: a) PhMe, 100 °C.

Scheme 17

The disconnections made in Parker's synthesis of morphine[22] show similarities

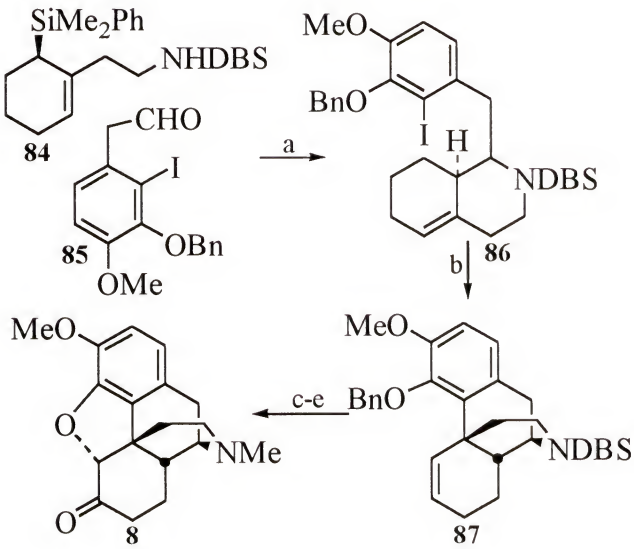


Conditions: a) PPh_3, DEAD; b) HF, MeCN; c) nBu_3SnH, AIBN, PhH, 130 °C; d) $Li/NH_3/^tBuOH$, THF, 0 °C; e) Swern oxidation.

Scheme 18

to those made by Fuchs[21] (Scheme 18). Phenol **80** and alcohol **81** were coupled under Mitsunobu conditions to give ether **82**. The TBDMS group was removed and a radical cascade sequence was performed in a sealed tube in the presence of nBu_3SnH to afford **83**. The tosyl group was removed generating a radical anion on the nitrogen which was subsequently trapped by the C9-C10 double bond to generate the D-ring. Finally, Swern oxidation afforded dihydrocodeinone **8**, thereby formalizing her synthesis.

Overman used a Grewe type disconnection in his synthesis of morphine (Scheme 19) but employed an intramolecular Heck reaction to make the C12-C13 bond.[23] Dimethylphenylsilyl protected amine **84** and aldehyde **85** were condensed in the presence of zinc iodide followed by iminium ion-allylsilane cyclization to afford **86**

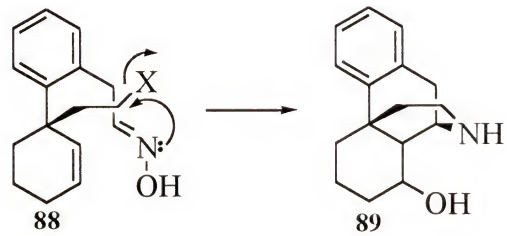


Conditions: a) ZnI_2, EtOH, 60 °C; b) Heck reaction; c) i. BF_3-Et_2O, EtSH; ii. (as camphorsulfonate), 3,5-dinitrophenylperbenzoic acid, CH_2Cl_2, 0 °C; d) NMO, TPAP; e) $Pd(OH)_2$, HCHO.

Scheme 19

(Scheme 19). Compound **86** underwent an intramolecular Heck reaction in the presence of $Pd(OCOCF_3)_2$ $(PPh_3)_2$ and 1,2,2,6,6-pentamethylpiperidine to give the morphinan **87**. Conversion to dihydocodeinone (**8**) through several more transformations formalized Overman's synthesis.

Parsons's group[24] had been working on a synthesis of morphine since the late 1970's, based on the idea shown in Scheme 20. The general idea was to alkylate oxime

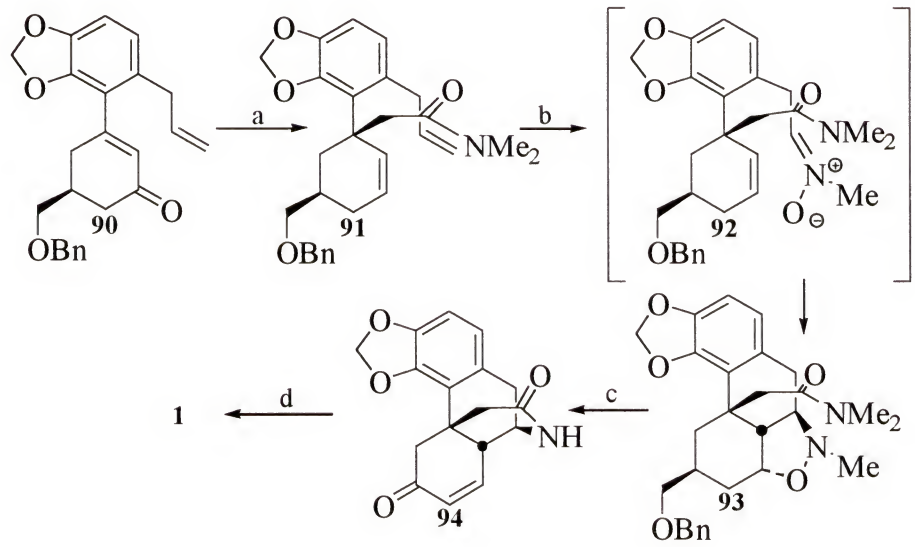


88 **89**

Scheme 20

88 to form the nitrone which would undergo a [3+2] dipolar cycloaddition in sequence to form the B- and D-rings of morphine (**89**). Despite unsuccessful attempts with this route, the Parsons group was able to build upon these results to develop a successful plan to synthesize morphine. Enone **90** underwent a Luche reduction followed by an Eschenmoser-Claisen rearrangement to set the quaternary center, **91** (Scheme 21). The double bond of **91** was cleaved oxidatively and treated with N-methylhydroxylamine to give the nitrone which underwent a [3+2] cycloaddition to the isoxazolidine **93**. The N-O bond and benzyl group were cleaved under reductive conditions, followed by cyclization of the HCl salt of the amino diol to the lactam which was then treated with

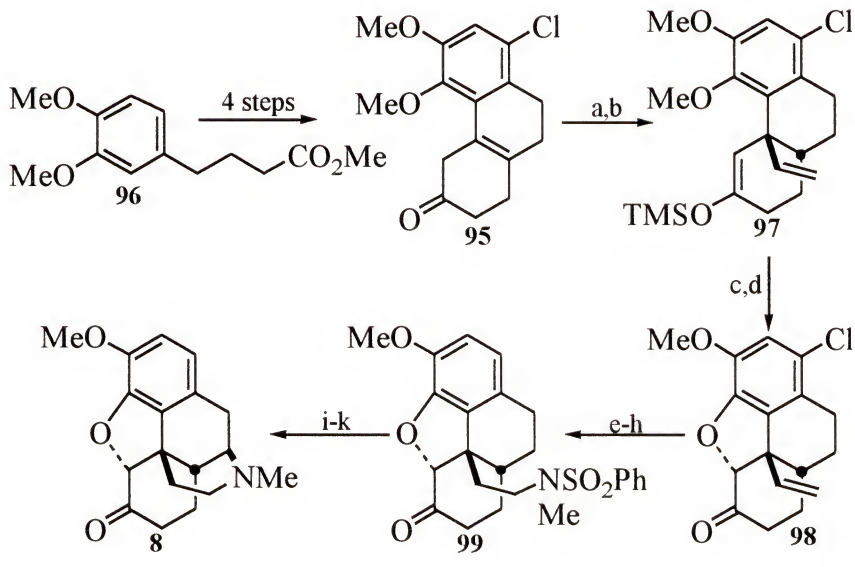
nitrophenylselenyl cyamide, then immediately oxidized to give enone **94**. Morphine (**1**) was generated after cyclization of the furyl ring and reduction of the enone.



Conditions: a) i. $NaBH_4$, $CeCl_3$; ii $MeC(OMe)_2NMe_2$; b) i. OsO_4; ii. $NaIO_4$; iii. MeNHOH,; c) i. H_2, $PdCl_2$; ii. HCl, heat in vacuum; iii. p-$NO_2C_6H_4SeCN$, Bu_3P, then H_2O_2; iv. O_3, Ph_3P; d) i. $CuBr_2$, MeCN, then KO^tBu; ii. $LiAlH_4$.
Scheme 21

In 1996, Mulzer and coworkers[25] published a formal total synthesis of morphine using a cuprate addition to a hydrophenanthrone to set the benzylic quaternary center of the compound (Scheme 22). The hydrophenanthrone **95** was synthesized in four steps from compound **96**. A vinyl cuprate addition in the presence of trimethylchlorosilane afforded compound **97**. α-Bromination followed by closure of the dihydrofuran ring by heating in DMF produced **98**. The chlorine atom was removed under hydrogenolysis and the nitrogen functionality was introduced through a hydroboration, oxidation,

Mitsunobu sequence to give **99**. Dihydrocodeinone **8** was formed from **99** by a method developed by Parker and Focas.[22]

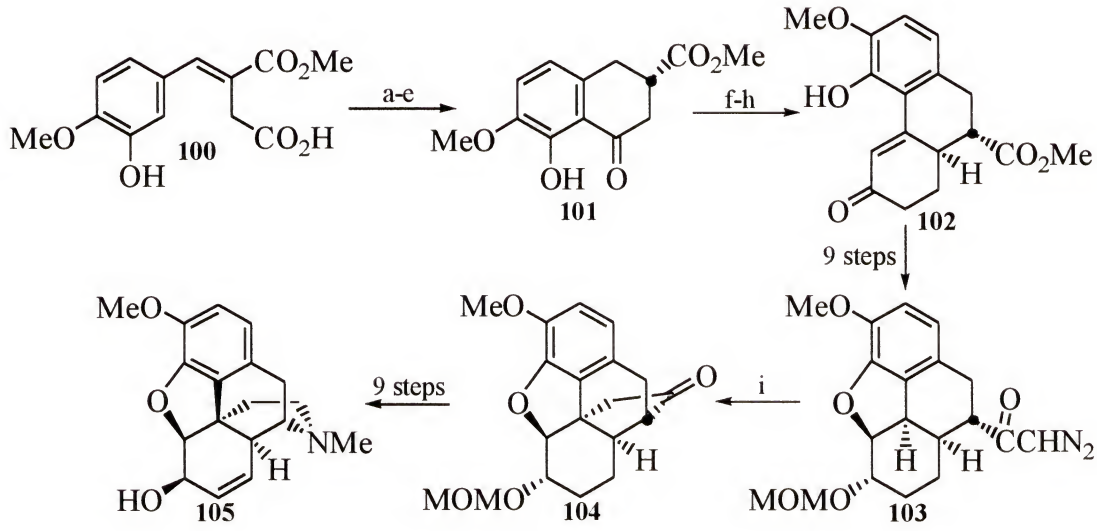


Conditions: a) $(CH_2CH)_2CuMgCl$, THF, -78 to 0 °C; b) TMSCl, Et_3N, 0 to 25 °C; c) NBS, THF; d) DMF, 140 °C; e) TMSCl, $(CH_2OH)_2$, CH_2Cl_2; f) i. BH_3SMe_2, THF; ii. H_2O_2, OH^-; g) Raney Ni, KOH, MeOH; h) $PhSO_2NHMe$, ADDP, BuP; i) NMS, $(PhCO_2)_2$, Et_3N; j) $Li/NH_3/^tBuOH$, THF; k) 3 N HCl, 90 °C.

Scheme 22

In 1997, White and coworkers[26] published a synthesis of the unnatural enantiomer of morphine based on a carbenoid C-H insertion (Scheme 23). Starting with cinnamate **100**, derived from isovanillin, an asymmetric hydrogenation, followed by bromination and an intramolecular Friedel-Crafts acylation gave tetralone **101**, in which formation of the undesired acylation product *para* to the phenol was blocked by the aryl bromide. Tetralone **101** was next treated with methyl formate, methyl vinyl ketone,

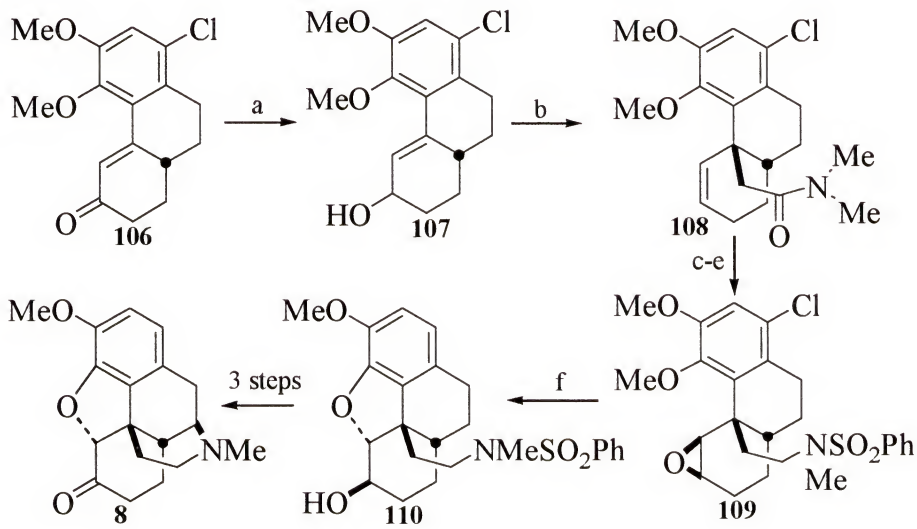
then subjected to base to form tricycle **102**. Several transformations were required to close the ether linkage and form diazo-ketone **103**. For White's key reaction, rhodium(II)-catalyzed carbenoid C-H insertion produced ketone **104**. Several more functional group transformations including a Beckmann rearrangement were required to produce (+)-codeine (**105**) which formalized his synthesis of (+)-morphine.



Conditions: a) H_2, $[Rh(COD)Cl_2]_2$, (4*R*, 5*R*)-(-)-MOD DIOP; b) Br_2, HOAc; c) MsOH, P_2O_5; d) H_2, Pd/C, $NaHCO_3$; e) LiOH, THF, H_2O; f) KH, HCO_2Me, DME, 0 °C; g) MVK, Et_3N, CH_2Cl_2; h) NaOH, H_2O, THF; i) $Rh_2(OAc)_4$, CH_2Cl_2.
Scheme 23

Mulzer and coworkers[27] published another approach to dihydrocodeinone **8** starting from the same starting precursor but using a Claisen-Eschenmoser rearrangement to set the stereochemistry at the benzylic quaternary center (Scheme 24). Enone **106**, derived from **96**, was reduced to give a mixture of diastereomeric alcohols, **107**. The desired alcohol was subjected to Claisen-Eschenmoser conditions to give **108**.

Now that the stereochemistry at the quaternery center of morphine was set, the dimethyl amide was converted to the sulfonamide and the double bond epoxidized with dimethyl dioxirane to afford epoxide **109**. Epoxide **109** was opened intramolecularly using the



Conditions: a) DIBAH, THF, -78 °C; b) $CH_3C(OMe),NMe_2$, PhMe, 110 °C; c) $LIBHEt_3$, THF; d) $PhSO_2NHMe$, ADDP, Bu_3P; e) oxone, CH_2Cl_2, 0 °C to room temperature; f) TFA, THF.

Scheme 24

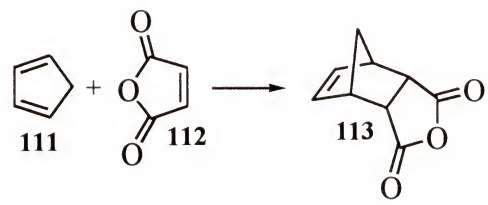
C4 methoxy substituent in the presence of TFA followed by subsequent deprotection to form the dihydrofuran ring (**110**). This compound was then converted to dihydrocodeinone **8** using the same sequence as previously reported.

Currently, there are 20 total or formal syntheses of morphine in the literature stretching from the early 1950's with Gates' pioneering synthesis to Mulzer's present day synthesis based on a sigmatropic rearrangement. Rice's 1980 morphine synthesis still remains the shortest and most economical synthesis among the 20 requiring 9 steps

to dihydrocodeinone in an overall yield of 29%. Unfortunately, Rice's synthesis still does not compete economically with the current method used to isolate morphine – extraction of the opium poppy seed – but even after 50 years research chemists are still trying to develop a short economical synthesis of morphine and its derivatives.

General Aspects of the Diels-Alder Reaction

One of the most widely used reactions to form substituted cyclohexene rings is the Diels-Alder reaction. In 1928, the reaction between cyclopentadiene (**111**) and



Scheme 25

maleic anhydride (**112**) was published by Otto Diels and Kurt Alder (Scheme 25).[28] They were able to determine the reaction's stereoselectivity and its generally accepted concerted nature before orbital symmetry was acknowledged. This reaction involving a

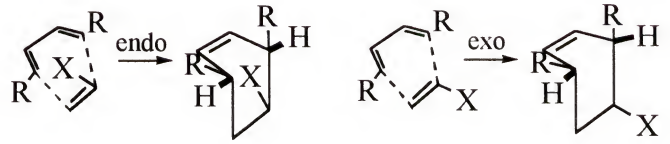


Figure 1 Transition states of the Diels-Alder reaction.

dienophile and a diene is classified as a [$\pi 4_s + \pi 2_s$] cycloaddition. The reaction is stereospecific and results in a syn addition with respect to the dienophile and diene. There are two possible orientations for unsymmetrical dienophiles, *endo* and *exo* (Figure 1). In the *endo* transition state the substituent X is oriented towards the π orbitals in the diene. While in the *exo* transition state, the substituent X is oriented away from the dienes π orbitals. When X = unsaturated substituents such as carbonyls, the *endo* transition state is usually preferred – commonly referred to as the Alder rule. Woodward and Hoffmann[29] explain the stabilization of the *endo* transition state using a secondary orbital overlap argument, which is between the π system in the diene and another π system that is in conjugation with the dienophile's double bond, this ultimately results in the stabilization of the *endo* transition state.

There are three types of Diels-Alder cycloadditions: 1) normal Diels-Alder

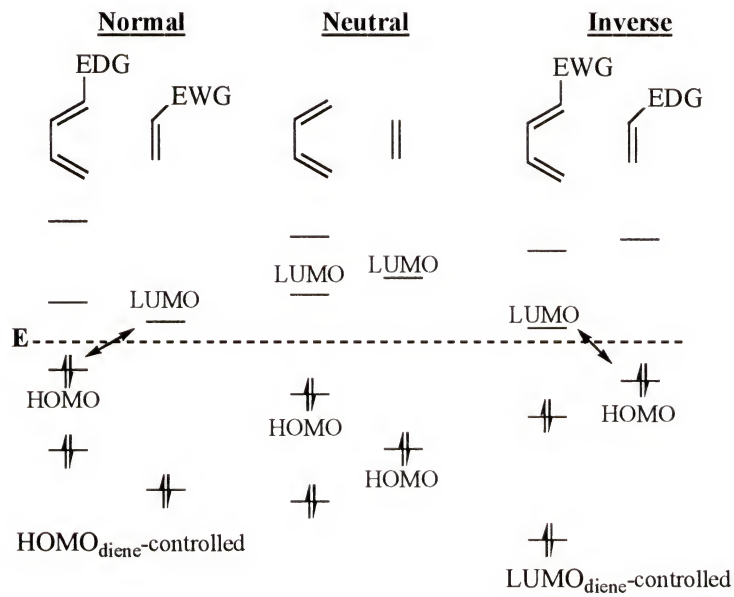


Figure 2[30] Energy diagram of the Diels-Alder cycloadditions.

reactions ($HOMO_{diene}$-controlled); 2) neutral Diels-Alder reactions; and 3) inverse demand Diels-Alder reactions ($LUMO_{diene}$-controlled). In the normal Diels-Alder reaction, which includes the majority of the Diels-Alder reactions, the electron rich diene system reacts with an electron deficient dienophile (Figure 2). The $HOMO_{diene}$ is raised and the LUMO of the dienophile is lowered thereby reducing the energy gap between the $HOMO_{diene}$ and $LUMO_{dienophile}$ when compared to the neutral case. In the inverse case,the LUMO of the diene is lowered while the HOMO of the dienophile is raised.

The regiochemistry, explained by frontier orbital theory, can also be predicted for unsymmetrical dienophiles. In the two cases seen in Figure 3, the HOMO of the diene and LUMO of the dienophile is the strongest interaction. Accordingly, the reactants will be lined up such that the carbons having the highest bonding coefficients in the two orbitals will begin the bonding process. In case A, C4 of the diene and C2 of the dienophile have the largest coefficients thereby producing the *"ortho"* cycloadduct.

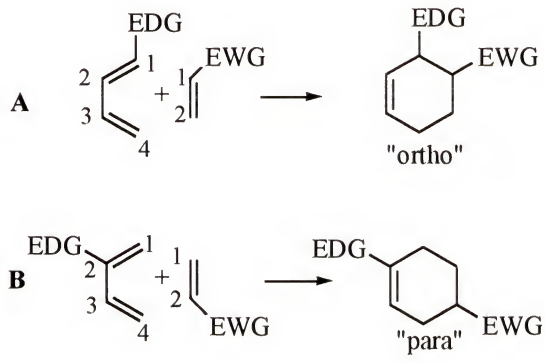


Figure 3 Regioselectivity of the Diels-Alder reaction.

In case B, C1 of the diene and C2 of the dienophile have the largest coefficients forming the *"para"* product.

General Aspects of the Intramolecular Diels-Alder Reaction

The intramolecular Diels-Alder (IMDA) reaction was not reported until three years after Diels and Alder were awarded the Nobel prize in 1950 for their work on the [4 + 2] cycloaddition. Alder had mentioned the reaction between 1,4-pentadiene and dimethyl acetylenedicarboxylate via an unisolated ene adduct to a bicyclo[4.1.0]heptane but never published it.[31] In the past 30 years there have been several examples of the

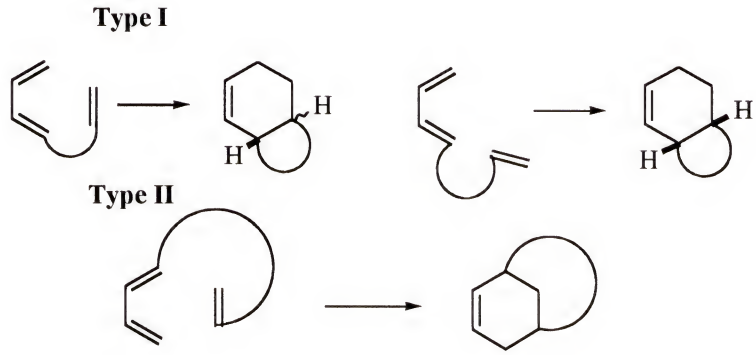
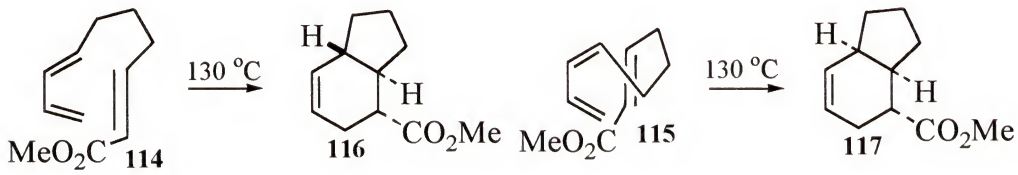


Figure 4 Intramolecular Diels-Alder reaction types.

IMDA reaction. Intramolecular Diels-Alder reactions form fused two ring systems and bridged ring systems in one chemical transformation. The length of the tether between the two reacting π systems controls the ring sizes of the two fused systems. It is also common to see high regio- and stereocontrol in the IMDA reaction. Intramolecular Diels-Alder reactions can be classified into two general groups: Type I and Type II that lead to fused and bridged systems respectively (Figure 4). The Type I systems give the fused ring systems for both (*E*)- and (*Z*)-dienes. The (*E*)-dienes give both *trans*- and *cis*-fused cycloadducts, while (*Z*)-dienes result only in *cis*-fused products.

IMDA Reactions Promoted by Thermal Conditions

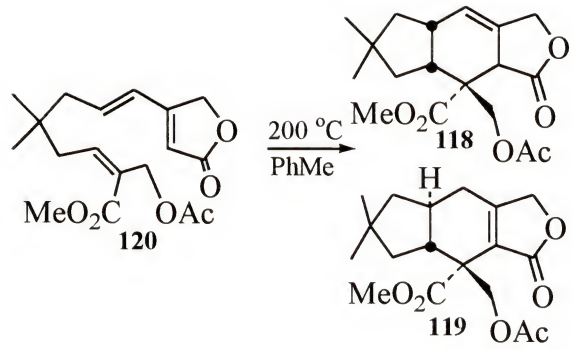
In 1965, House and coworkers[32] published the first systematic investigation of the IMDA reaction by studying trienes **114** and **115** (Scheme 26). Heating of triene **114** led to the *trans*-fused hydrinane derivative **116** while treatment of triene **115** under the



Scheme 25

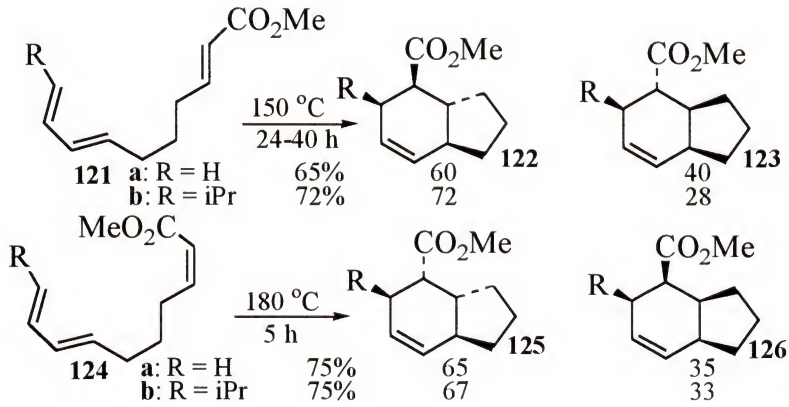
same conditions led to only the *cis*-fused hydrinane derivative **117** which can be explained by considering the transition state that would lead to the *trans* fused product was too highly strained.

Boeckman and Ko[33] found that the Alder *endo* rule is not always followed when they obtained a 1:1 mixture of cycloadducts **118** and **119** from the IMDA reaction of **120** (Scheme 27). Roush had also noted this with an earlier study of cycloadducts possessing perhydroindan nuclei.[34] They both suggested that an alternative model for describing the IMDA reaction's transition state was needed since secondary orbital interactions was not a factor anymore. Instead nonbonding interactions and conformational preferences of the tether played a larger role in the nature of the transition state.



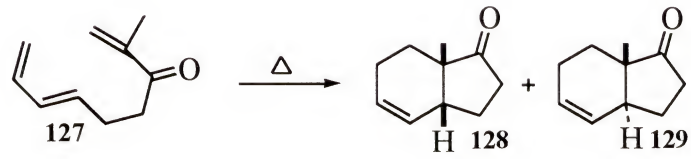
Scheme 27

Roush investigated a series of nonatriene systems (Scheme 28).[35] His group found that the major products from these cyclizations were the *trans*-fused cycloadducts, clearly opposite of what the Alder *endo* rule would predict. Even the dienophile geometry did not have any influence on the product distribution, leading to the assumption that secondary orbital interactions were not the primary controlling factors.



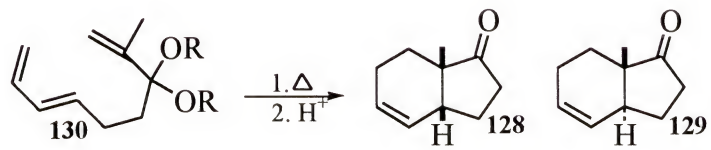
Scheme 28

Bajorek and Sutherland published in 1975[36] that heating triene **127** in a degassed



Scheme 29

solution of benzene afforded compound **128** as the major product (Scheme 29). Jung and Halweg[37] repeated this experiment several years later under several different

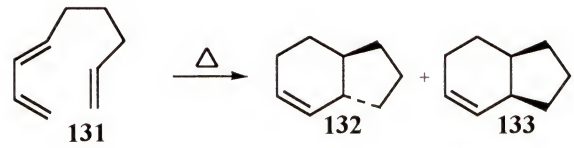


Scheme 30

conditions and found that a ratio of 70:30 (**128**:**129**) was obtained (Scheme 29). They also found that they could invert this ratio by ketalizing the carbonyl group (**130**) as seen in Scheme 30. Making the carbonyl group more sterically demanding than the methyl group reversed the stereoselectivity.

In 1985, Wu and Houk[38] published the IMDA cyclization of unactivated triene **131** and found that thermal cyclization afforded a ratio of 25:75 **132** to **133** (Scheme 31). These results were in contrast to Roush's terminally substituted triene results.[35]

Houk reported a 1 kcal/mol preference for the thermodynamic product over the kinetic product.



Scheme 31

Houk then published a communication[39] addressing the stereochemical outcome of these IMDA reactions. His "twist-asynchronous" model proposed that the stereochemistry is controlled by the timing of bond formation in the transition state. For example, substituent X at the terminal end of the dienophile increases the LUMO coefficient of C2 compared to C1. Frontier molecular orbital theory proposes that C2-C6 bond formation would be more complete in the transition state as compared with the

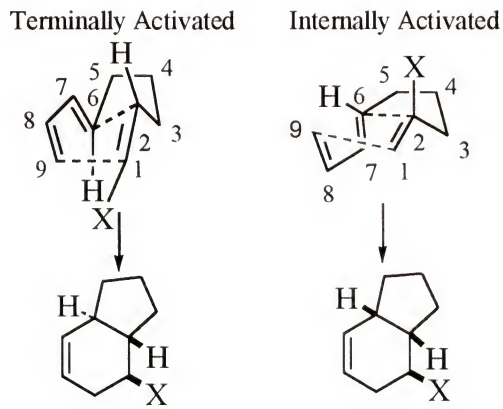
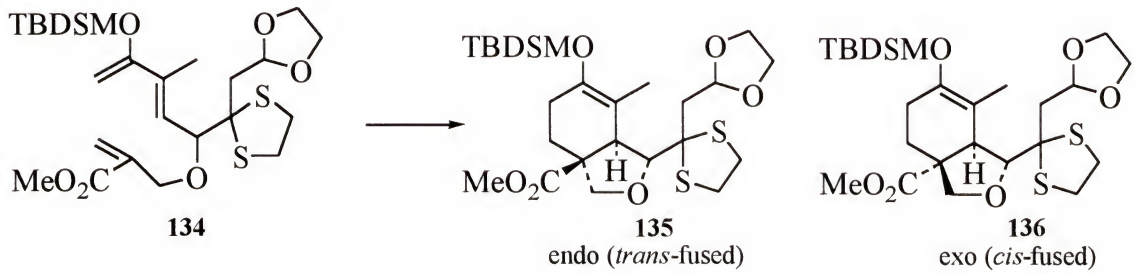


Figure 5 Houk's "twist-asynchronous" model.

C1-C9 bond, causing the triene to "twist" during the transition state that leads to the *trans*-ring fusion. The opposite effect is seen for the internally activated dienophile, so that the "twist" contribution is not as substantial, which was seen in his earlier communication.[38]

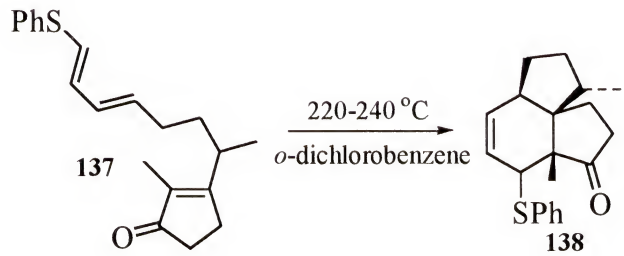
That Houk's model does not apply to all cases was demonstrated by Jung and Halweg's paper[37] discussed previously in which they ketalized the carbonyl group of **130** (Scheme 30) and reversed the product ratio to favor the *trans*-fused ring system. Here is was assumed that steric interactions of the ketal groups dominated the outcome. Another IMDA cyclization that did not follow the "twist-asynchronicity" pattern was published by Ley and coworkers in 1988.[40] The internally activated triene, **134**, underwent cyclization to give the *trans*-fused ring system **135** as the predominant product (62% *trans*-fused **135** and 23% *cis*-fused **136**), most likely resulting from the steric bulk encountered in the *cis*-like transition state (Scheme 32).



134 **135** endo (*trans*-fused) **136** exo (*cis*-fused)

Scheme 32

In 1987, Fukumoto and coworkers[41] cyclized triene **137** to the *cis*-fused tricycle **138** exclusively via an *exo* transition state (Scheme 33). The reasoning behind this was because of steric interactions between the two methyl groups in the potential *endo* transition state.



Scheme 33

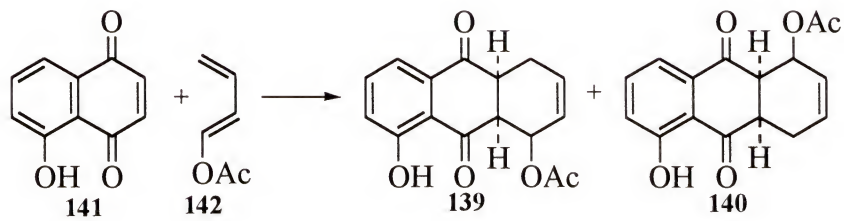
There are a wide variety of conditions used for inter- and intramolecular Diels-Alder reactions. The use of thermal energy is the most common method for carrying out both types of reactions. In the case of intramolecular Diels-Alder reactions, the majority of the examples use thermal conditions. The temperatures required for these cycloadditions vary with the types of substituents on the triene and are difficult to predict.

IMDA Reactions Promoted by Lewis Acid Catalysis

The use of Lewis acids to catalyze Diels-Alder reactions was first noted in 1960 by Yates and Eaton.[42] They saw increases in the reaction rates of maleic anhydride, dimethylfumarate, benzoquinone with anthracene and dimethylnaphthalene with maleic anhydride when they used aluminum chloride at room temperature. Diels-Alder reactions not only show increased rates under mild conditions under Lewis acid

catalysis but they also show differences in stereo- and regioselectivity when compared to their thermal counterparts. Lutz and Bailey[43] proposed that the catalytic activity is a result of complex formation between the Lewis acid and the dienophile. When this occurs, the dienophile's LUMO is lowered by the Lewis acid, which lowers the energy gap with the HOMO of the diene.

The stereochemistry of the reaction can still be predicted by the Alder *endo*-rule and the *cis*-rule. Frequently, the *endo*:*exo* ratio is often increased in the presence of



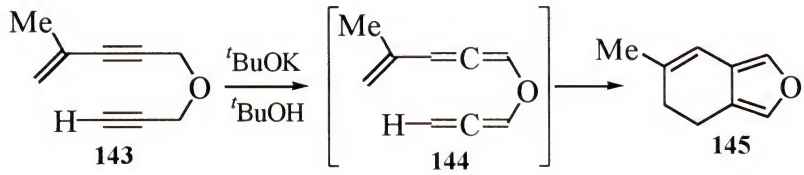
Scheme 34

Lewis acids. Trost and co-workers[44] showed that under thermal conditions the ratio of **139** to **140** was 3:1 (Scheme 34). The use of 5 mol% $BF_3{\cdot}Et_2O$ resulted in predominantly **139** at room temperature.

The enantioselectivity in asymmetric reactions can also be controlled by Lewis acids. With the Lewis acid as the source of chirality, the complex with a functionalized dienophile can control the facial selectivity of the reaction. The result of the reaction also depends on whether the Lewis acid is syn or anti to the double bond of the dienophile.

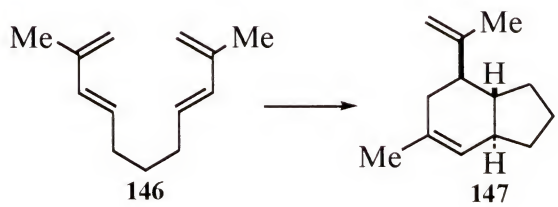
IMDA Reactions Promoted by Acidic or Basic Conditions

Both acid and base have been used to promote IMDA reactions. Ollis and co-workers[45] used *t*-BuOK to generate the bisallene **143** which cyclized to give 6-methyl-4,5-dihydroisobenzofuran (**145**) (Scheme 35). In 1984, Gassman and Singleton[46] showed that substrate **146** did not show any cyclization products under thermal



Scheme 35

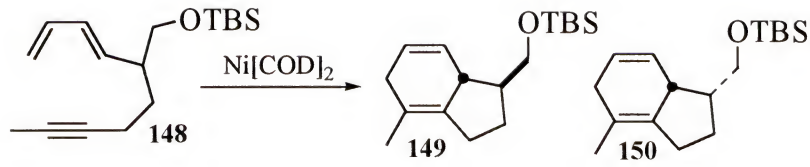
conditions. Treatment with $HSbCl_6$ or CF_3SO_3H resulted in the formation of **147** in 42% and 88% yields respectively (Scheme 36).



Scheme 36

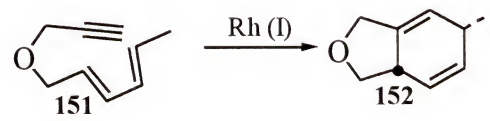
IMDA Reactions Promoted by Transition Metals

The use of transition metals has also been used to catalyze relatively unactive triene systems. Wender and Jenkins[47] reported the use of nickel (0) to catalyze the



Scheme 37

cyclization of dienyne **148** to give the 1,4-cyclohexadienes **149** and **150** (Scheme 37). Livinghouse and co-workers[48] showed the cyclization of similar substrates using a Rh (I) complex (Scheme 38). His communication reported the cyclization of terminal



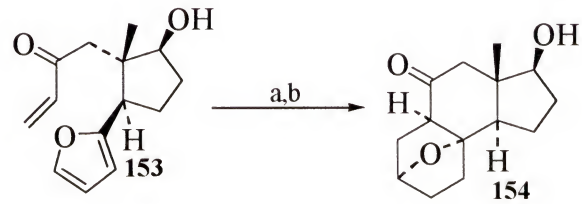
Scheme 38

alkynes and alkenes (**151**) to give the corresponding cycloadducts (**152**) with high diastereoselectivity.

IMDA Reactions Promoted by Nonconventional Methods

Rideout and Breslow reported the cyclization of cyclopentadiene and butenone in aqueous solution in 1980.[49] He showed that the rate was substantially increased under these conditions. The rate acceleration was a result of a "hydrophobic effect" which causes the nonpolar molecules to aggregate in order to reduce the hydrocarbon-water interfacial area. He was also able to show these rates increase even more using LiCl to cause the nonpolar compounds to "salt out" of solution resulting an increase in

aggregation. Another way to increase the rate was provided by means β-cyclodextrins which provide a cavity where the diene and dienophile could aggregate. DeClercq and

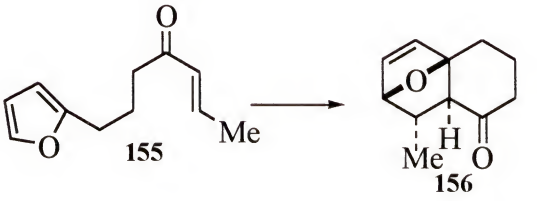


Conditions: a) H_2O, room temperature, 30 minutes; b) H_2O-MeOH, H_2, Pd-$BaSO_4$
Scheme 39

co-workers published an example of an IMDA reaction in 1985 using the furan derivative **153** (Scheme 39).[50] The furanic diene **153** underwent the [4 + 2] cyclization in water at room temperature after 30 minutes to afford the tricycle **154**.

High pressure can be used to perform Diels-Alder reactions in the cases of thermally unreactive dienes because of steric hindrance or thermal instability of a substrate or product. The first high pressure intermolecular Diels-Alder reaction was reported by Dauben and Krabbenhoft in 1976 for monoactivated dienophiles and substituted furans.[51] Since that time, there have been several examples of inter- and intramolecular Diels-Alder reactions utilizing high pressure. The majority of the IMDA reactions involve the use of furan dienes. The aromaticity of the furans tends to shift the equilibrium ratio toward the starting materials, which can be overcome by standard Diels-Alder conditions already discussed, but these methods do not always work efficiently. High pressure shifts the equilibrium by accelerating only the forward reaction to the cycloadducts as seen by Keay and Dibble in 1989.[52] When the furan

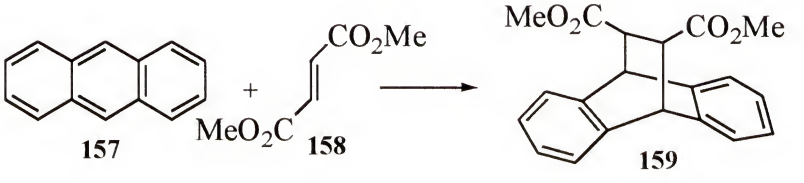
precursor **155** was exposed to Florisil in methylene chloride, no reaction was observed. Treating it with 2.0 M $CaCl_2$ for 4 days resulted in a 4:1 ratio of product **156** to starting



Scheme 40

material (Scheme 40). However, at 12.5 kbar they were able to convert all of the starting material to product in one day.

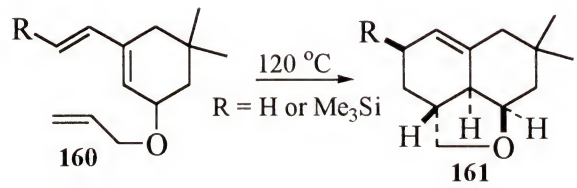
The use of microwave ovens in organic synthesis was reported in 1986.[53] Later that same year, Majetich and coworkers[54] reported several Diels-Alder reactions using microwave ovens to enhance the reaction rates. The reaction between anthracene (**157**)



Scheme 41

and methyl fumarate (**158**) which gave the cycloadduct **159** in a 90% yield after 72 hours at 101 °C, gave a yield of 87% in 10 minutes at 325 to 361 °C in *p*-xylene using a microwave oven (Scheme 41).

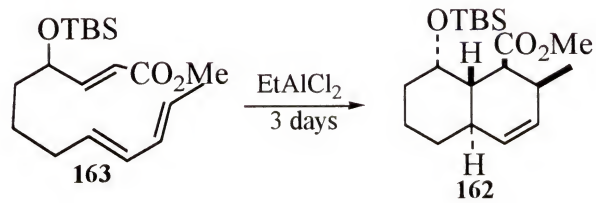
Ollis's paper[45] using a *t*-BuOK catalyzed isomerization of enyne **143** to generate the bisallene **144** which underwent an IMDA reaction to give the dihydroisobenzofuran **145** (Scheme 35) is one of the first reported ether tethered IMDA reactions. While working on nagilactone model systems, Burke and coworkers[55] designed triene **160**



Scheme 42

which they cyclized at 120 °C over 67-70 hours as a neat liquid to give yields of the cycloadduct **161** in ranges of 63-82% (Scheme 42).

In 1982, Funk and Zeller[56] were able to construct the decalin derivative **162** in

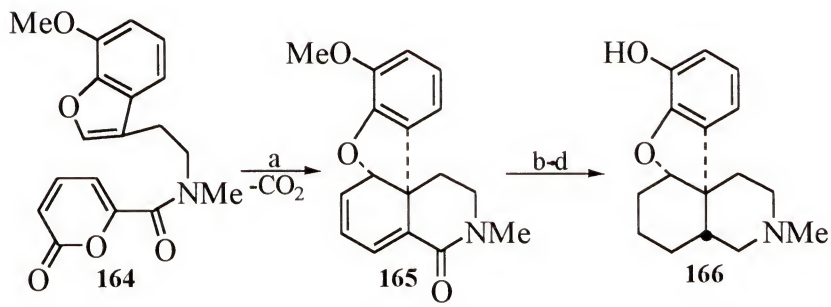


Scheme 43

high yields, using a Lewis acid catalyst, exclusively as one isomer while working on a synthesis of compactin (Scheme 43).

IMDA Approaches to Morphine

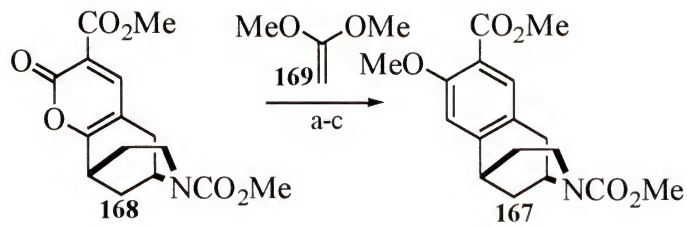
In 1981, Ciganeck[57] was the first to report the construction of morphine fragments via an intramolecular Diels-Alder reaction of benzofuran derivative **164**. Compound **164** was heated under reflux in 1,2,4-trichlorobenzene for 10 hours to afford the benzofuro-isoquinoline, **165** (Scheme 44). Catalytic hydrogenation followed by reduction of the lactam and demethylation produced morphine fragment **166** in 86% yield from **164**.



Conditions: a) 1,2,4-trichlorobenzene, reflux, 10 hours; b) H_2, Pd/C; c) BH_3-SMe_2; d) nPrSK, DMF.

Scheme 44

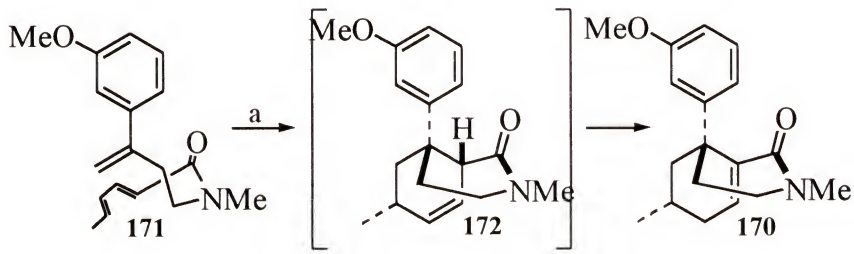
Boger and coworkers[58] used an inverse demand Diels-Alder reaction to a racemic benzomorphan **167** in high yield (Scheme 45). Treatment of the 3-carbomethyoxy-2-pyrone, **168**, with 10 equivalents of 1,1-dimethylethylene, **169**, in toluene (120 °C, 1 h, 97%) followed by ester hydrolysis, decarboxylation, and phenol demethylation gave the benzomorphan **167** in 97% yield.



Conditions: a) MePh, 120 °C, 10 eq. **169**; b) 0.67 N NaOH, THF, 25 °C, 1 hour; c) Cu, quinoline, 22 °C; 1 hour.

Scheme 45

Williams and coworkers[59] constructed morphinan skeletons of the type **170** in order to study their analgesic properties. In refluxing DMSO the intramolecular Diels-

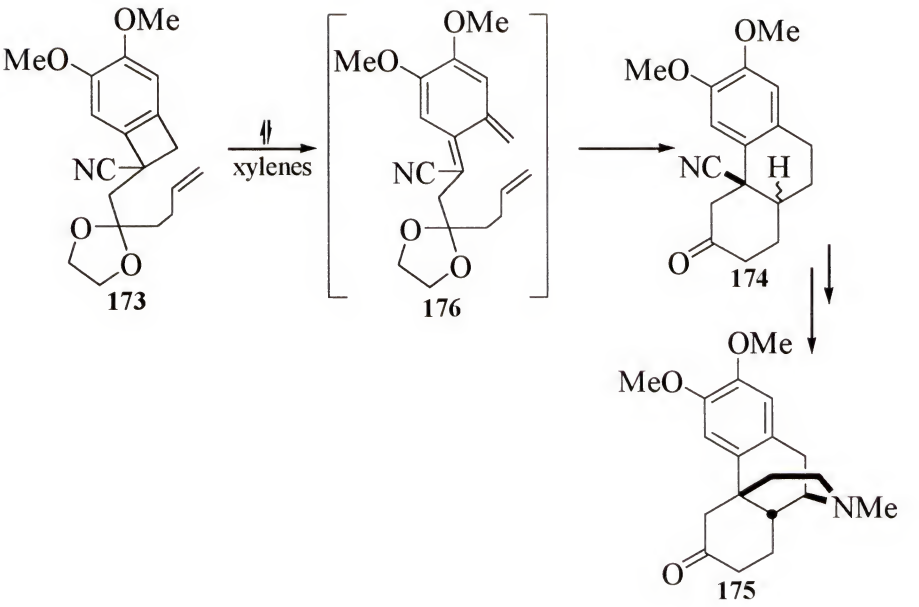


Conditions: a) DMSO, reflux, 24 hours.

Scheme 46

Alder reaction of triene **171** was assumed to go through an *endo* transition state to form the *trans*-fused intermediate **172** which rearranged to give the 4a-aryloctahydroisoquinoline system **170** (Scheme 46).

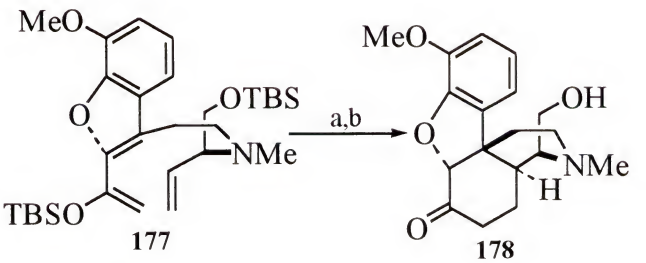
Kametani and coworkers[60] used a benzocyclobutene derivative **173** as their source of the ABC ring system of morphinans. Thermolysis of **173** in refluxing xylene produced a mixture of the *cis*- and *trans*-cycloadducts (**174**) in 61% and 29% yields



Scheme 47

respectively (Scheme 47). They were able to employ the cyano appendage through several chemical transformations to form the D-ring of the morphinan (**175**) for the *cis*-cycloadduct.

Constanzo[61] constructed an IMDA precursor **177** from *o*-vanillin and (*S*)-(+)-methionine in 13 steps. Rings A, C, D and O were formed from the thermal cyclization

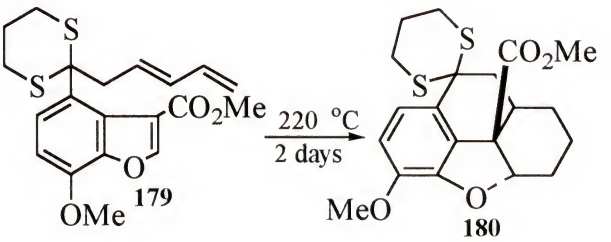


Conditions: a) 214 °C, 24 hours; b) TBAF.

Scheme 48

of the precursor to give **178** (Scheme 48). Low yields from the IMDA reaction prevented the final ring closure of C10-C11 in order to complete the synthesis of the morphine skeleton.

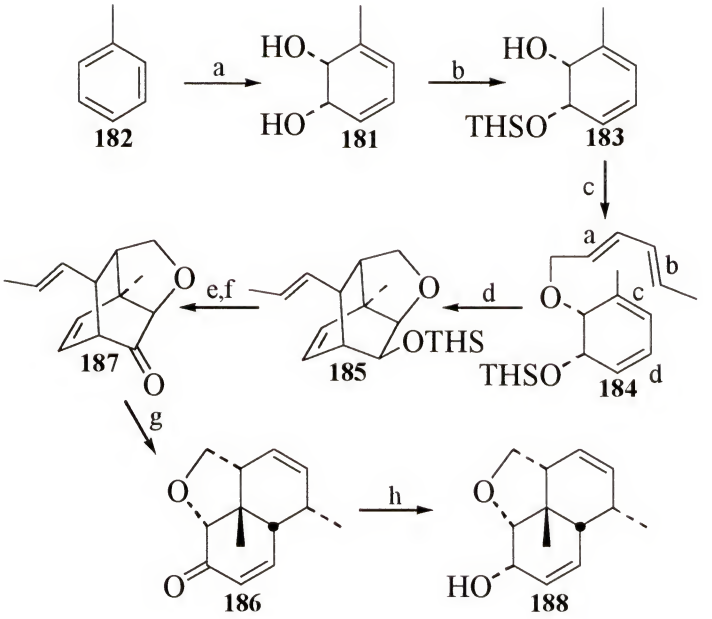
Also using an IMDA approach, Wu[62] put together the B and C rings of morphine



Scheme 49

using benzofuran derivative **179** (Scheme 49). A geminal dithiane was also used to assist the IMDA reaction through a Thorpe-Ingold effect. The ester (**180**) was reduced with DIBAL to give a mixture of the primary alcohol and aldehyde (3:1) but installation of the nitrogen and closure of the D-ring were not reported.

Hudlicky, Boros, and Boros published a combined microbial oxidation, intramolecular Diels-Alder cycloaddition followed by a Cope rearrangement to form the B-, C-, and O-rings of morphine in 1992.[63] Starting with the microbial oxidation product **181** of toluene (**182**), the distal hydroxyl group was protected as the dimethylthexylsilyl ether **183** (Scheme 50). The allylic hydroxyl was alkylated with sorbyl bromide to afford the tetraene **184**. For the IMDA reaction there were two possible pathways that the cycloaddition could take. One of them would have consisted of diene a,b with dienophile c (Scheme 50). The other involved the combination of

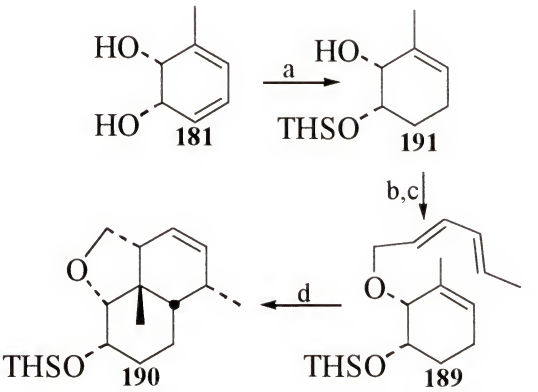


Conditions: a) toluene dioxygenase; b) THSCl, imidazole, DMF; c) NaH, sorbyl bromide, THF, 0 °C then room temperature, 30 h.; d) CCl_4, 77 °C, 7 h.; e) nBu_4NF-$3H_2O$, THF; f) PCC, CH_2Cl_2, room temperature; g) xylenes, sealed tube, 250 °C, 22h.; h) $NaBH_4$, $CeCl_3$-$7H_2O$, MeOH, room temperature, 15 min.

Scheme 50

dienophile a and diene c,d. The latter was observed to afford compound **185**. Attempts to force this compound to undergo a Cope rearrangement to form the desired tricyclie **186** failed. The simplest method in order to create some sort of driving force for the Cope rearrangement was to be able to generate an enone during the Cope rearrangement. Removal of the silyl group followed by oxidation produced ketone **187**. The ketone underwent Cope rearrangement thermally to afford enone **186** with the desired framework. Reduction of **186** under Luche conditions gave compound **188** which resembled the lower half of morphine. The reduced form of the tricycle was also obtained through a simpler model study in which the disubstituted double bond of diol

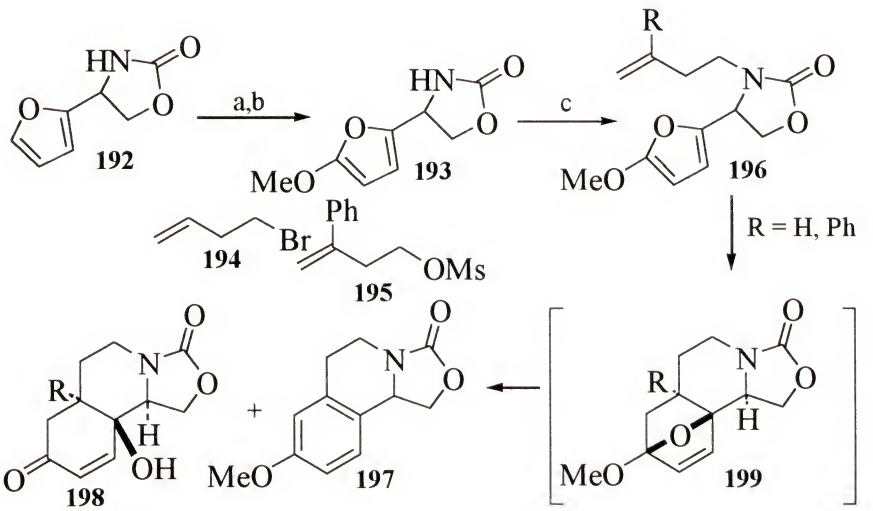
181 was reduced with diimide to avoid the regioselectivity problem (Scheme 51). Through the same protection, alkylation sequence as above, triene **189** was produced. Because of the stereospecificity of the biooxidation, the diene tether was delivered from the α face of the compound during the IMDA



Conditions: a) PAD, AcOH; b) THSCl; c) NaH, sorbyl bromide; d) 210 °C, PhMe
Scheme 51

reaction. The tricycle **190**,which is similar to tricycle **188**, resulting from the thermal cyclization is another example of the construction of the nonaromatic portion of morphine. Unfortunately, compounds **188** and **190** were never compared chemically, which would become evident during future investigation into this methodology. All of the stereocenters were set correctly, except for what would be C9 of morphine; however, this center is set correctly for an S_N2 reaction from a nitrogen appendage from C13 of morphine which would form the D-ring of morphine. A second generation model study using this idea and the IMDA methodology was done later.

In 1995, Hudlicky and coworkers[64] published an advanced IMDA study using substituted furans as the dienes (Scheme 52). Starting from the known oxazolidinone **192** the methoxy substituted furan **193** was prepared via a bromination/elimination sequence. Compound **193** was N-alkylated using alkene **194** or **195** to form the dienophile tether **196**. The unsubstituted dienophile was cyclized at 120 to 165 °C to

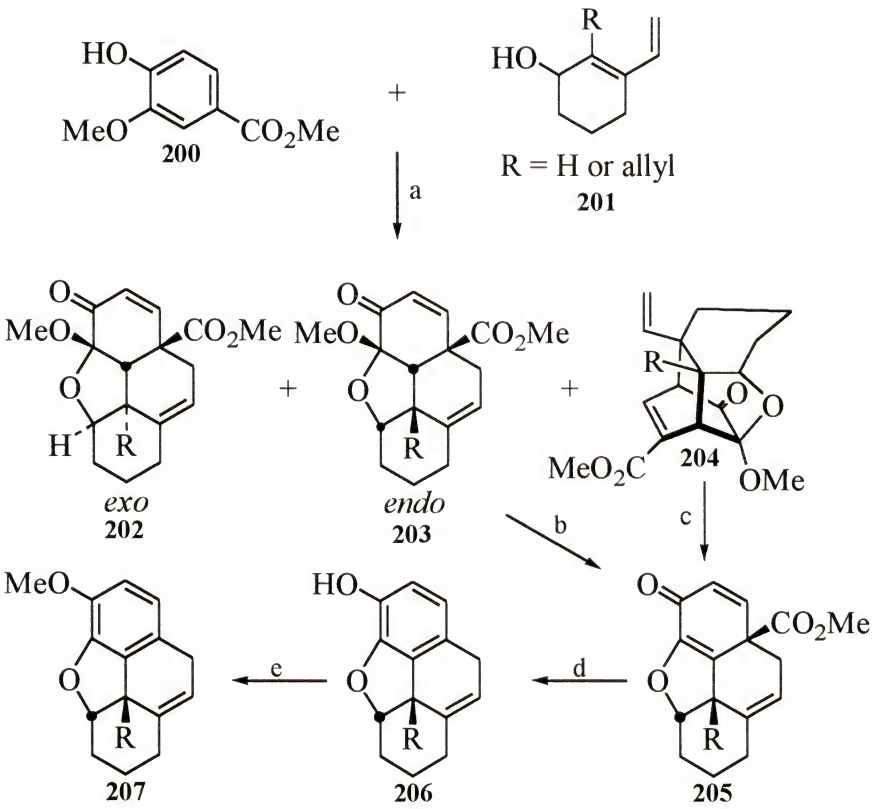


Conditions: a) Br_2, MeOH; b) CSA, heat; c) NaH, DMSO, **194** or **195** (for R = H, PhH, sealed tube, 120 to 165 °C, **197**, 40 %; **198**, 55%; for R = Ph, PhMe, sealed tube, >250 °C, **198**, 13%.

Scheme 52

give a mixture of Diels-Alder adducts **197** and **198** (40% and 55% respectively). When the phenyl substituted dienophile was cyclized thermally in toluene, only one adduct was formed, **198**, in yields around 10%. This study showed that it was possible to construct functionalized isoquinolines using the IMDA reaction of substituted furans.

Similar to the Hudlicky, Boros and Boros study,[63] the Rodrigo group[65] synthesized a morphinan via IMDA cycloaddition followed by a Cope rearrangement (Scheme 53). Starting with a mixture of methyl vanillate (**200**) and three equivalents of 3-vinyl-cyclohex-2-enol (**201**) in the presence of bis(triflouroacetoxy)iodobenzene, three Diels-Alder adducts were produced (**202-204**). The bridged heterocycle **204** underwent a Cope rearrangement thermally to give the phenanthrofuran system **205**.

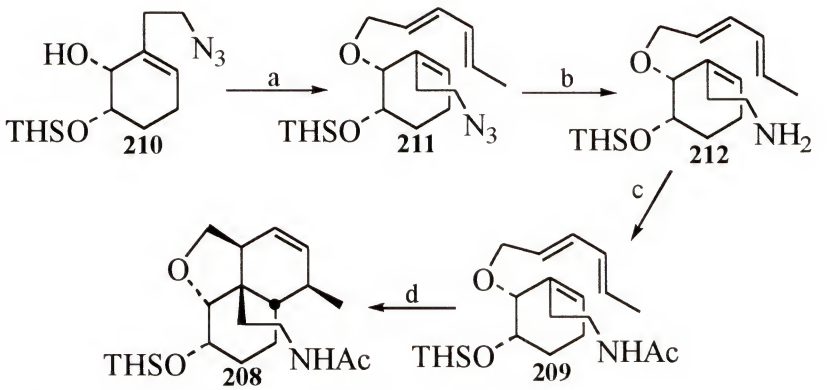


Conditions: a) bis(trifluoroacetoxy)iodobenzene; b) trifluoroacetic acid; c) $Cl_2CHCHCl_2$, heat; d) NaOH, MeOH; e) K_2CO_3, Me_2SO_4, acetone.

Scheme 53

This was saponified and decarboxylated to give the morphinan **206**. Morphinan **206** could also be derived from the *endo* isomer via treatment with trifluoroacetic acid to produce intermediate **205**. The *exo* isomer **202** was stable to prolonged acid treatment.

Hudlicky and Gum[66] published a second generation IMDA approach toward morphinan skeletons in 1998 (Scheme 54). This generation was to include a nitrogen

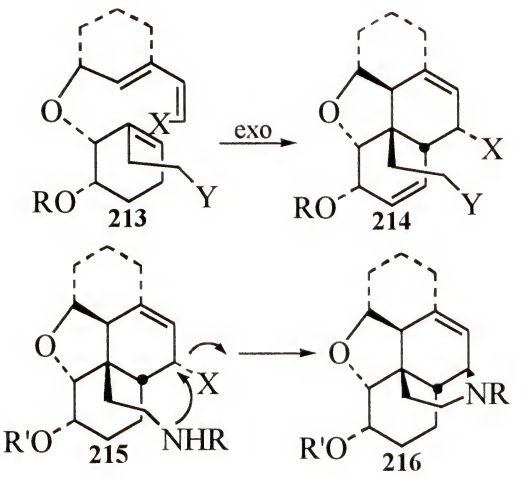


Conditions: a) NaH, sorbyl bromide; b) PPh_3, THF, THF; c) Ac_2O, pyridine; d) 230 °C; PhMe.

Scheme 54

appendage from the quaternary carbon of the tricycle **208** that would be used to form the D-ring of the morphinan skeleton. It was found during the cyclization of the triene **209** that the stereochemistry at the C9 of tricycle **208** was "up" instead of "down" as was reported earlier[63] leading to the conclusion that the transition state of the IMDA reaction proceeded through an *exo* transition state and not an *endo* one. (The mistake would have been avoided if the spectral data of the fully reduced structures resulting from further transformations of **188** and **190** had been compared). With these results in mind, a third generation approach using the IMDA reaction methodology has been

developed. Knowing that the (*E,E*)-diene system of both the Boros' and Gum's model study gives the stereochemistry as seen for tricycle **208** (Scheme 54), it is envisioned that an (*E,Z*)-diene system of the type **213** (Scheme 55) will lead to an inversion of



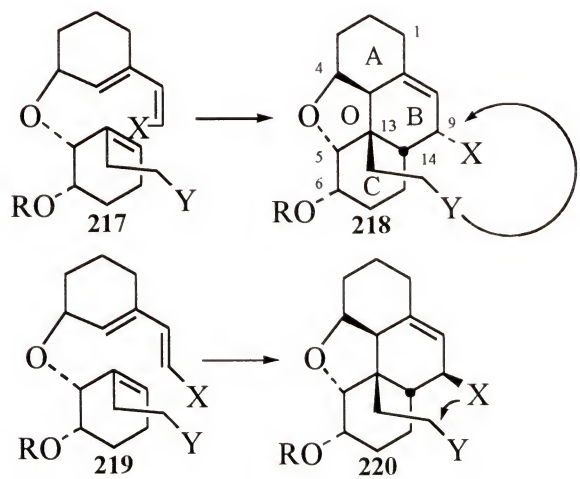
Scheme 55

stereochemistry at the C9 position to afford compounds of the type **214**. A nucleophilic substitution reaction by the N-appendage would then be set up to occur at the C9 position of **215** (Scheme 55) to form the D-ring **216** of the morphine skeleton. These ideas will be further elaborated in the Results and Discussion chapter.

CHAPTER 3
RESULTS AND DISCUSSION

Introduction

There are twenty or so published syntheses of morphine,[7] none of which use an inter- or intramolecular Diels-Alder (IMDA) reaction as a key step. While examples of the IMDA reaction have been used in approaches towards morphine, none of these have resulted in successful total synthesis. In this third generation model study, an IMDA reaction is to be used to set three of the five chiral centers (C14, C13, & C9, morphine numbering) and construct the O- and B-rings of the morphine skeleton in one step (Scheme 56). The other two stereocenters (C5 and C6) will be formed using an enzymatic dihydroxylation. Based on previous model studies,[63,66] it is assumed that the



Scheme 56

(*E,Z*)-diene system (**217**) will result in an Diels-Alder adduct with the C9 stereochemistry as shown (**218**). All of the previous model studies[63,66] have shown that the (*E,E*)-diene systems (**219**) have resulted in Diels-Alder adducts with the stereochemistry for C9 as shown on structure **220**. This methodology should provide a new novel route to morphine and morphinan derivatives.

Model studies performed in the Hudlicky laboratories[63,66] have shown that the IMDA reaction of **221** will afford the B,C and O rings of the morphine skeleton (**222**) shown in Equation 1 of Figure 6. The stereocenters set during the IMDA reaction correspond correctly to those of the natural isomer of mophine (C13, C12, and C9).

The original model study[63] used an IMDA reaction followed by a Cope rearrangement to construct tricycle **186** shown in Equation 2 of Figure 6. Triene **184** was constructed by selectively protecting the biooxidation product of toluene as the dimethylthexylsilyl ether followed by O-alkylation with sorbyl bromide. Upon refluxing in CCl_4, the Diels-Alder adduct **185** was formed. After desilylation, oxidation, and thermal rearrangement, tricycle **186** was produced.

This tricycle was also formed through a shortened sequence.[63] The disubstituted double bond of the diene diol **181** was reduced with diimide (Equation 3, Figure 6) followed by protection of the distal hydroxyl group. Next, the allylic hydroxyl was alkylated as discussed before to afford the triene **189** and finally **189** was cyclized thermally to give tricycle **190**.

The stereochemistry which is shown for tricycle **190** was determined using nOe coupling experiments. The centers at C13 and C12 (morphine numbering) were set correctly for the natural isomer of morphine but the C9 center was inverted which was

proven wrong later in the second generation study. Performing a couple of simple transformations on compounds **186** & **190** and comparing their products could have

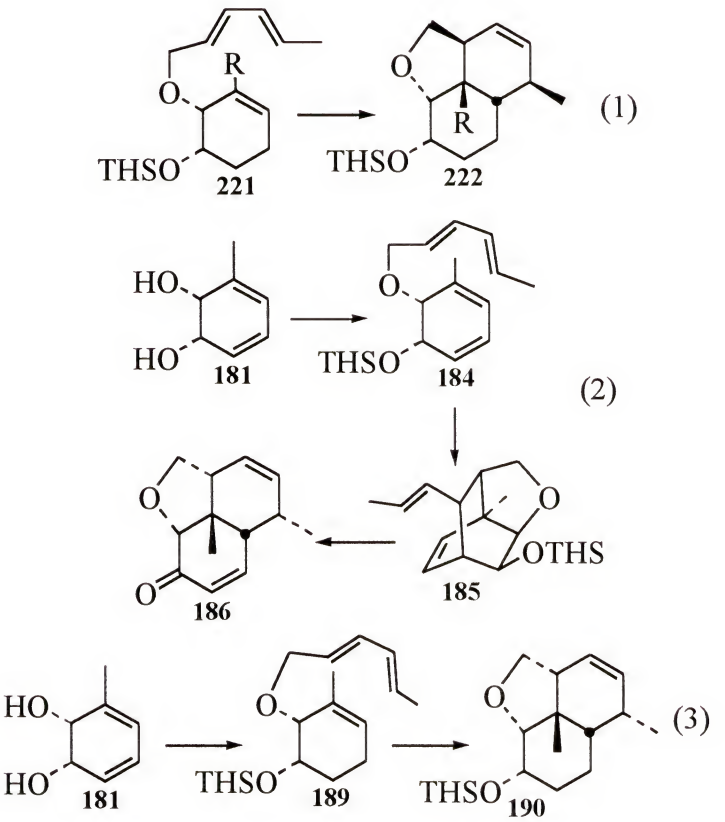
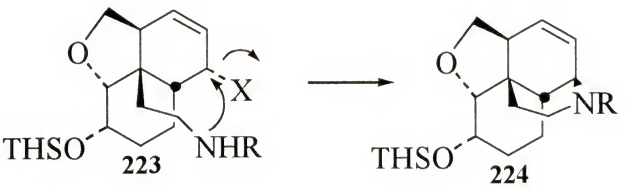


Figure 6. Development of advanced generation IMDA approach.

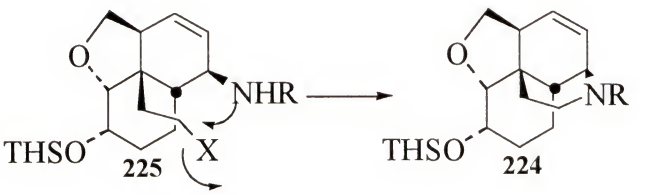
prevented this mistake. If **186** & **190** were to have the same stereochemistry then hydrogenation of **186** and oxidation/hydrogenation of **190** should result in the same product. Nevertheless, a second generation approach was developed based on the assumed results of the first generation model study.

The next generation of this model study was to incorporate an appendage with some sort of functionality that could be used to form the D-ring of the morphine skeleton. For example, as shown in Scheme 57, a nucleophilic nitrogen is at the end of



Scheme 57

the two-carbon appendage (**223**) and the C9 position is electrophilically activated using a good leaving group. The C9 leaving group could then be envisioned to undergo a nucleophilic attack by the nucleophilic nitrogen to form the D-ring of the morphine skeleton with the correct stereochemistry (**224**). Alternate approach can be envisioned



Scheme 58

in Scheme 58 in which the nucleophilic groups are switched (**225**). For example, the leaving group would be part of the 2-carbon appendage and the nucleophilic nitrogen would be attched to the ring. Nucleophilic substitution onto the 2-carbon appendage

would also lead to the formation of the D-ring of the morphine skeleton (**224**). Such strategy served as insurance against the operation of "mixed" transition states during the Diels-Alder reaction and the C9 stereochemistry would then become the function of geometry of the terminal olefin.

In the second generation synthesis, triene **209** constructed from azidoethyl diene diol was cyclized thermally to give tricyclie **208** (Figure 7). When the spectral data of

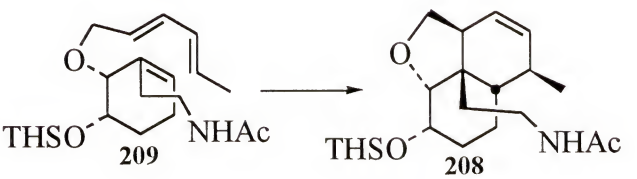
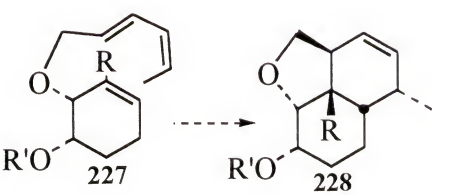


Figure 7. Development of synthetic strategy: Second generation model study.

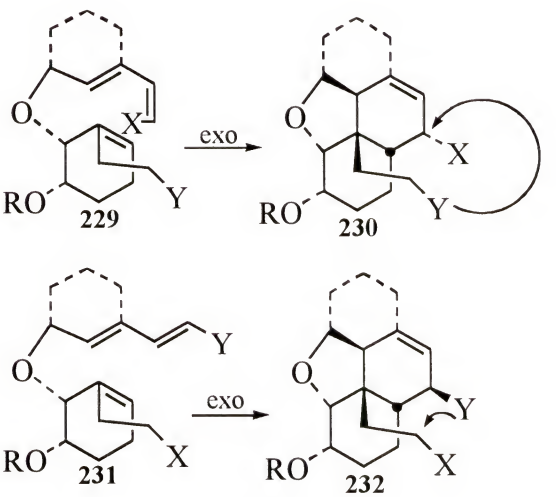
tricycle **208** was compared to that data of the first generation tricyclies, the data did not match. The stereochemistry of the Diels-Alder adduct was discovered to be different from that previously reported. By means of an X-ray crystal structure, the C9 stereocenter was found to be β instead of α as originally determined by the nOe



Scheme 59

experiments. So, the transition state of the IMDA reaction was now assumed to go through an *exo* transition state. It was also assumed that since the (*E,E*)-diene gives the stereochemistry shown for compound **208** (Figure 7), an (*E,Z*)-diene (**227**) should give stereochemistry in which the C9 position is inverted (**228**) (Scheme 59).

The above analysis led to the development of a third generation approach to the morphine skeleton using an IMDA reaction. Since the (*E,E*)-diene system of **209** gives the tricycle **208** with the reported stereochemistry as shown in Figure 7, in which the



Y = nucleophile X = leaving group

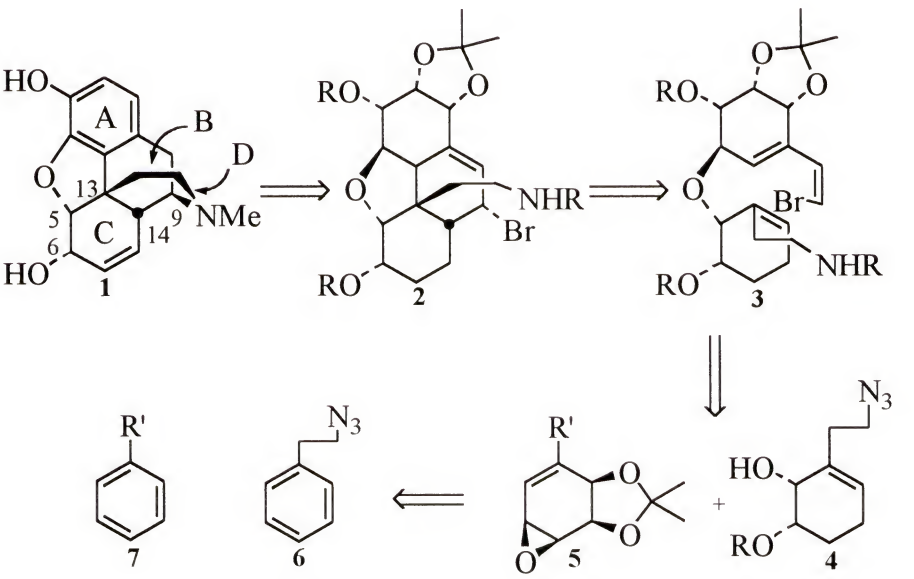
Scheme 60

C9-methyl group is "up." So, investigation into whether or not an (*E,Z*)-diene system will result in the opposite stereochemistry at the C9 position will be studied. If successful, then the next step will be to determine the conditions necessary for an S_N2 substitution to take place at the C9 center (ie. **230**) or from the nucleophile at the C9

position (**232**) in order to form the D-ring of the morphine skeleton (Scheme 60). Also, another ring is to be incorporated into the synthesis which will eventually become the A-ring of the morphine skeleton. With this in mind a synthetic plan was devised as shown in Scheme 1.

Synthetic Plan

The original synthetic plan of this project can be seen in Scheme 1. Ultimately, the target compound of this project is tetracycle **2**. From here a simple substitution of



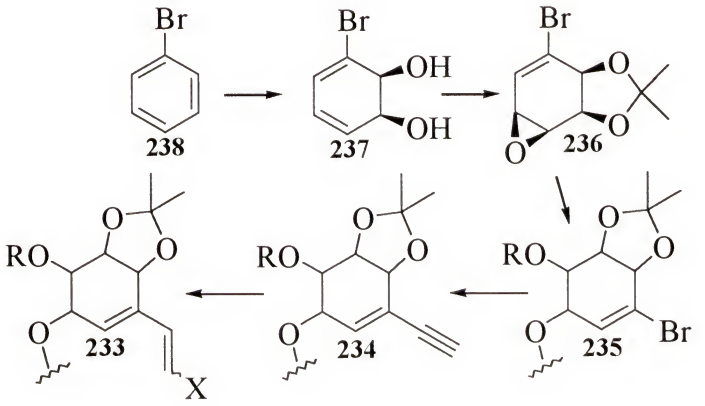
R = Bn, R' = Br or (*E*)- & (*Z*)-CHCHBr

Scheme 1

the C9 position would give the entire skeleton of morphine. This tetracycle is to be formed via the IMDA reaction of triene **3**. From what has been shown by the past two IMDA model studies, the (*E,Z*)-stereochemistry of the diene **3** should give the Diels-Alder adduct **2** with the desired stereochemsitry at C9. The triene **3** can be formed

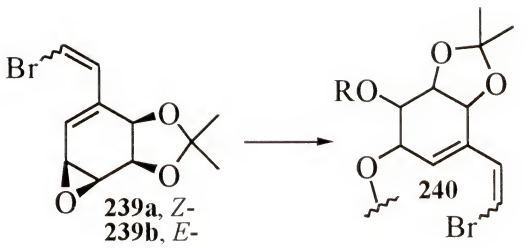
through the coupling of the substituted epoxide **5** and the azidoethyl diol **4**. These two compounds are in turn derived from the biooxidation products of their respective aromatic compounds (**6** & **7**).

The additional ring, which would eventually become the A-ring of the morphine skeleton, also contained the diene for the Diels-Alder reaction. Two methods were considered in order to install the vinyl group onto "ring-A." One involved constructing



Scheme 61

the vinyl group of the diene (**233**) from an acetylene (**234**) attached to the vinylbromide **235** via a Sonogashira coupling and hydroboration sequence to afford the diene **233** (Scheme 61). The other method had the vinyl group already in place as in the β-bromostyrene epoxide **239** (Scheme 62). At the time of this analysis, β-bromostyrenes **241** were not known substrates for the toluene dioxygenase mediated biooxidation, nevertheless it was assumed that the enzyme would oxidize such compounds since styrenes in general undergo biooxidation.

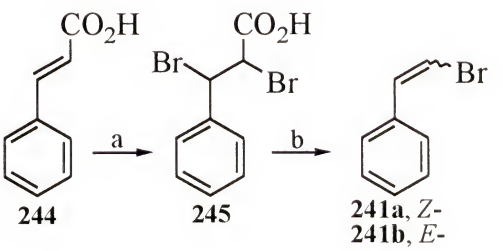


Scheme 62

Synthesis of Substrates for Biooxidation

Both the A- and C-rings for this morphine synthesis are to be derived from the biooxidation products of bromobenzene **238** or β-bromostyrene **241** and bromoethylbenzene **242** or azidoethylbenzene **243**. Bromobenzene **238** and bromoethylbenzene **242** were purchased commercially. Azidoethylbenzene **243** was synthesized via a nucleophilic substitution of bromoethylbenzene **242** using sodium azide (Scheme 68).

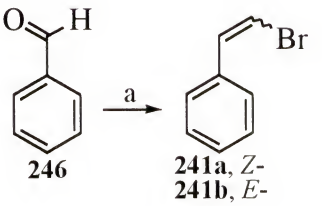
Several methods used were tested in order to synthesize the substrates (*E*)- and (*Z*)- β-bromostyrene (**241a** & **241b**) needed to test the biooxidation. Bromination of



Conditions: a) Br_2, *hv*, $CHCl_3$; b) NaOEt, EtOH, heat.

Scheme 63

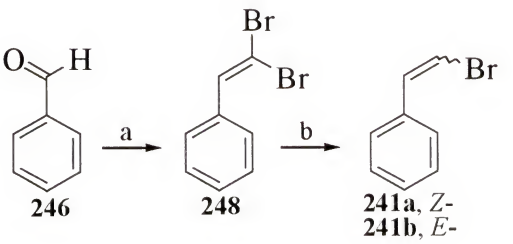
cinnamic acid **244** provided the dibromide **245** (Scheme 63) which was eliminated using NaOEt in absolute EtOH to give an 80:20 (*Z*:*E*) β-bromostyrene mixture (**241a**:**241b**).[67] The ratio could be reversed by using NaOH in H_2O for the elimination



Conditions: a) $(Ph_3PCH_2Br)Br$ (**2487**), ^tBuOK, THF.
Scheme 64

reaction. Another method used a Wittig reaction between benzaldehyde **246** and ylide **247** (Scheme 64).[68,69] A ratio of β-bromostyrene (85:15, **241a**:**241b**) was formed, similar to the bromination elimination sequence of cinnamic acid (Scheme 63).

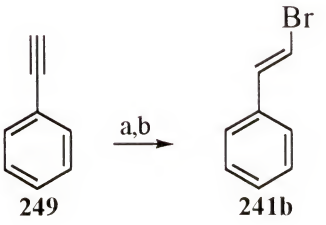
In order to obtain pure samples of (*E*)- and (*Z*)-β-bromostryene **241a** and **241b** several methods were used. Treating benzaldehyde **246** with CBr_4 in the presence of



Conditions: a) CBr_4, PPh_3; b) nBuSnH, $Pd(OAc)_2$.
Scheme 65

PPh_3 afforded the vinyl dibromide[70] **248** which was reduced in the presence of nBu_3SnH[71] and $Pd(OAc)_2$ to give predominantly (*Z*)-β-bromostyrene **241a** (99:1, *Z*:*E*) (Scheme 65). The other method to give predominantly (*E*)-β-bromostyrene **241b** used phenylacetylene **249** as the starting material (Scheme 66).[72]

Hydroboration of the acetylene **249** followed by aqueous workup afforded the (*E*)-boronic acid which was treated with N-bromosuccinimide in acetonitrile to give the vinyl bromide **241b** with retention of configuration. Because of its ease to scale-up and



Conditions: a) catecholborane, heat, then H_2O; b) NBS, MeCN.
Scheme 66

the decent yields, the Wittig sequence (Scheme 64) was the preferred method to obtain large quantities of the *Z*-β-bromostyrene **241a**. The biooxidation of these substrates and structure proofs of the metabolites are discussed below.

Isolation and Characterization of Metabolites

The starting materials used for this synthesis are derived from the whole cell biooxidation products of substituted aromatics (Figure 8). These bacterial cells have been engineered to express the enzyme toluene dioxygenase which is responsible for the

biooxidation.[73] This enzyme is one of several responsible for the degradation of substituted aromatics found in the soil to catechol which is then cleaved to eventually

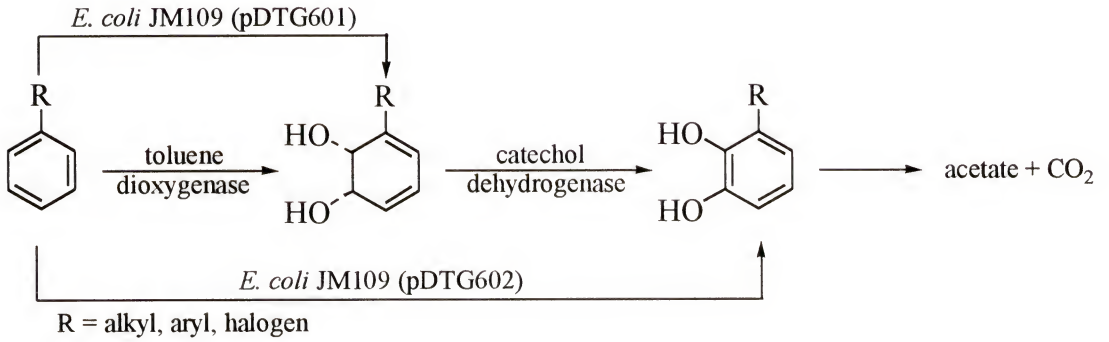


Figure 8. Biodegradation of substituted aromatics.

give carbon dioxide and acetate. In the late 1960's, Gibson and coworkers discovered a blocked mutant strain of *Psuedemonus putida* that was able to grow using toluene as its sole carbon source to form the corresponding *cis*-diene diols in enantiomeric excesses of >99%.[73] They determined that the enzyme toluene dioxygenase was necessary for this biooxidation and the genes responsible for the formation of this enzyme were later found and cloned into *E. coli* JM109. Currently, this biooxidation is the only method which gives these *cis* diene diols in high enantiomeric excess. In 1995, Motherwell and Williams[74] published a catalytic photoinduced charge-transfer osmylation, the chemical alternative to the biooxidation. While the latter reaction may be experimentally simpler, the product is a mixture of racemic isomers in low yields.

All five of the *cis*-diene diols used for this project were obtained in quantitative yield from the biooxidation (Table 1).[75] The yields for the azidoethyl diol **251** were

lower than those derived for the bromoethyl diol **250** presumably because of the toxicity of the azide toward the bacterial cells. The β-bromostyrenes **241a** and **241b** were fed to the fermentation broth neat as a mixture of (*E*)- & (*Z*)-isomers to give their respective diols **252a** and **252b** in yields of around 1 g/L of broth. The two resulting diols (**252a** & **252b**) were separated via preparative HPLC eluting with a 25:75 acetonitrile:H_2O mixture to give the (*E*)-isomer **252b** as a white solid ($[\alpha]_D^{23}$ = 83.1, c = 0.75 $CHCl_3$) and the (*Z*)-isomer **252a** as a slightly yellow oil ($[\alpha]_D^{25}$ = 40.3, c = 1.0 $CHCl_3$)

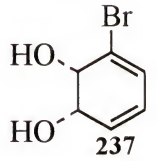
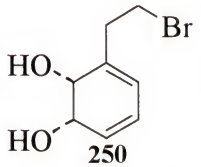
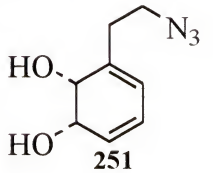
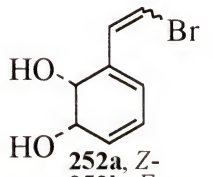
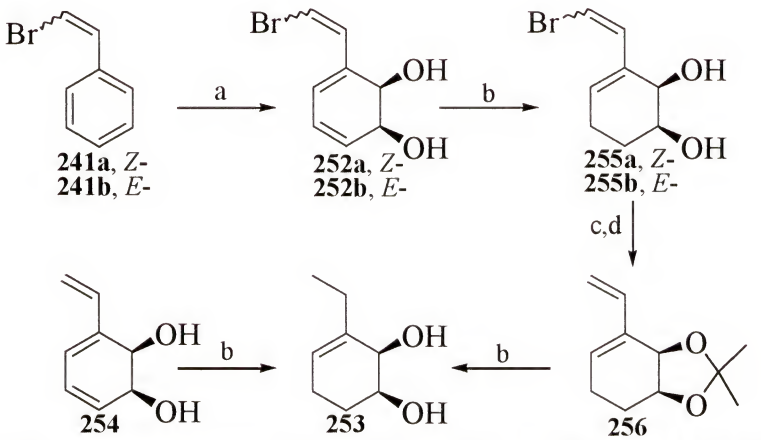
Diol	Yield	Ref.
 **237**	9 g/L	76
 **250**	200 mg/L	77
 **251**	40%	78*
 **252a**, *Z*- **252b**, *E*-	1 g/L	79

Table 1 Biooxidation yields. * Yield (%) of oxidation multiplied by yield (%) of protected diol (set at 95%).

Both of the diols (**252a** & **252b**) were converted into a common intermediate[79] **253** which was also derived from the known metabolite of styrene[80] (**254**) (Scheme 67).



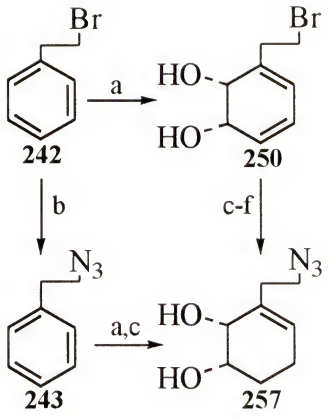
Conditions: a) toluene dioxygenase; b) PAD, AcOH, MeOH; c) DMP, *p*-TsOH, CH_2Cl_2; d) ^{t}BuLi, THF, -78 C, then NH_4Cl; e) HCl, MeOH.

Scheme 67

The mixture of diols (**252a** and **252b**) underwent a diimide reduction to reduce the less substituted endocyclic bond to give diols **255a** and **255b**. The diols **256a** and **256b** were then protected as the acetonide and dehalogenated via a metal-halogen exchange followed by an ammonium chloride quench to give diene **256**. The vinyl group was then reduced using potassium diazocarbodiimide then deprotection of the acetonide afforded diol **253** which matched the diol obtained from the diimide reduction of styrene diol **254**.

First Synthetic Approach - Bromobenzene as Latent Ring A

The dienophile unit was to be the same as used for the 2nd generation synthesis. Starting with bromoethylbenzene **242** or azidoethylbenzene **243**, the desired azidoethyl diene diol **257** was synthesized.[78] As seen in Scheme 68, a nucleophilic substitution

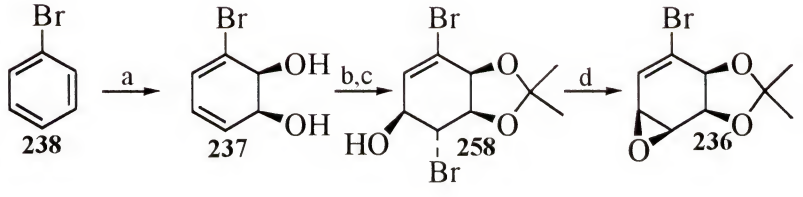


Conditions: a) toluene dioxygenase; b) NaN_3, DMF; c) PAD, AcOH, MeOH; d) DMP, *p*-TsOH, CH_2Cl_2; e) NaN_3, DMF; f) HCl, MeOH.

Scheme 68

using sodium azide in DMF to form the azidoaromatic **243** can be done before the biooxidation. An alternate route starts with the biooxidation of bromoethylbenzene **242** to the *cis*-diene diol, followed by a diimide reduction, protection, substitution and deprotection sequence to give **257**. Both methods give similar overall yields of 20-30% from bromoethylbenzene **242**.

The bromoepoxide **236** was synthesized in three steps from the bromodiene diol **237** (Scheme 69).[81] The diol **237** was protected as the acetonide then converted into the

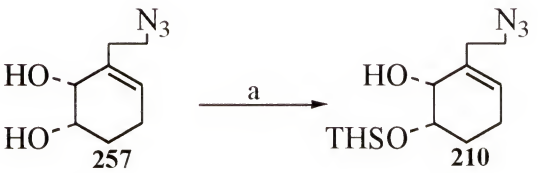


Conditions: a) toluene dioxygenase; b) DMP, *p*-TsOH, CH_2Cl_2; c) DBH, acetone, H_2O; d) 10% NaOH, DME.

Scheme 69

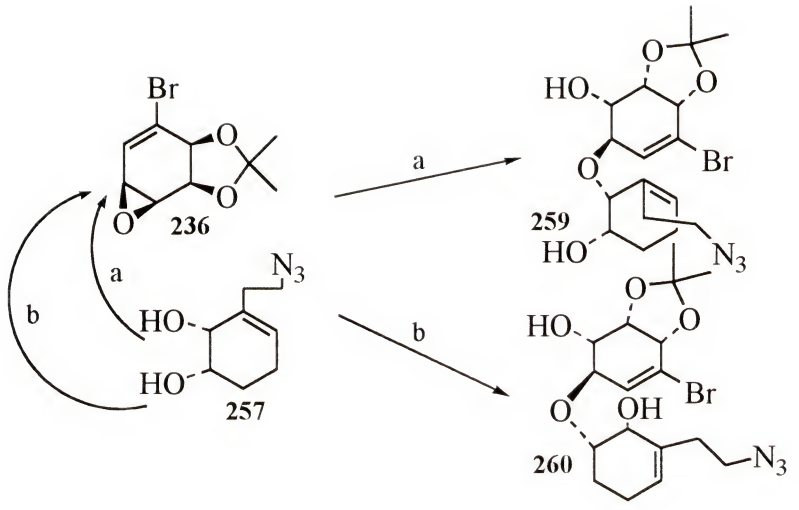
bromohydrin **258** using 1,3-dibromo 5,5-dimethylhydantoin. Upon, treatment with 10% NaOH, the bromohydrin **258** was cyclized to the syn epoxide **236** in overall yields of 60%.

The distal hydroxy group of the azidoethyl diol **257** was next protected using a dimethylthexylsilyl group (Scheme 70) to afford alcohol **210**. Originally a

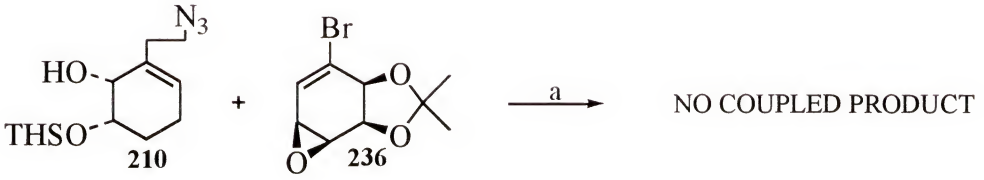


Conditions: a) dimethylthexylsilyl chloride, imidazole, DMF, 0 °C.
Scheme 70

dimethylthexylsilyl group was used to avoid the undesired coupling product (**260**) (Scheme 71). As seen in the two previous IMDA approaches this reagent was used because of its effect on regioselectivity, a result of its bulkiness. Unfortunately, its size was a negative influence during the Lewis acid mediated coupling reaction between the epoxide **236** and alcohol **257** (Scheme 72). A smaller protecting group was needed but as the group decreases in size so does the regioselectivity. Our attention then turned to using a benzyl protecting group derived from the reduction of the corresponding benzylidene **261**.



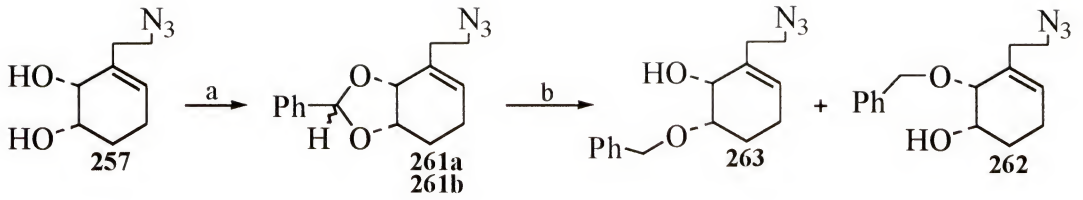
Scheme 71



Conditions: a) BF_3-Et_2O, CH_2Cl_2, room temperature, 5-6 days.

Scheme 72

Treatment of diol **257** with benzaldehyde **246** in the presence of *p*-toluenesulfonic acid afforded the benzylidene (**261a** and **261b**) as a diastereomeric mixture (Scheme 73). This mixture was separable using preparative HPLC and the stereochemistry at the benzylic position was assigned using an nOe difference experiment (see Appendix A for spectra). Reduction using sodium cyanoborohydride and titanium tetrachloride[82] led to the two alcohols **262** and **263** in a ratio of 1.5 to 1 respectively, the minor being of the desired isomer. Both were separable using standard



Conditions: a) PhCHO, *p*-TsOH, CH_2Cl_2; b) $NaCNBH_3$, $TiCl_4$, MeCN.

Scheme 73

flash silica gel chromatography and both isomers were assigned structures (Figure 9) using an nOe difference experiment as well as TOCSY and HMQC 2D experiments.

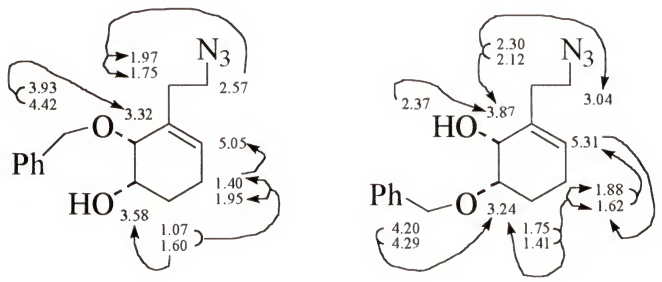
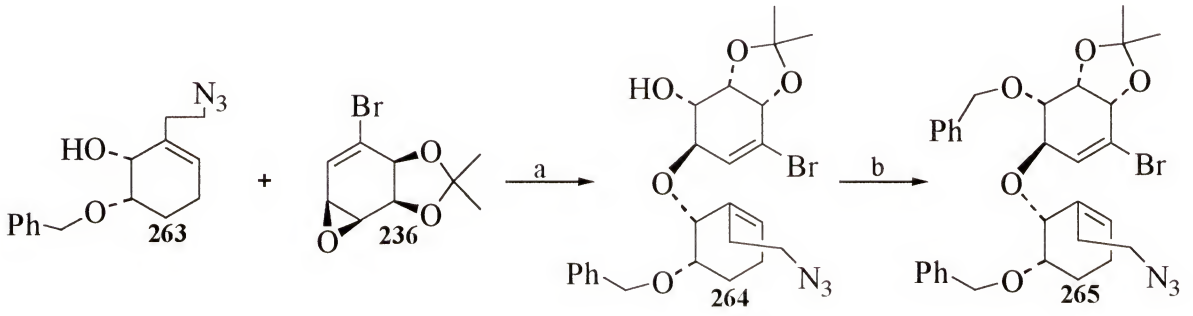


Figure 9. Structure determination of azido alcohols **262** and **263**.

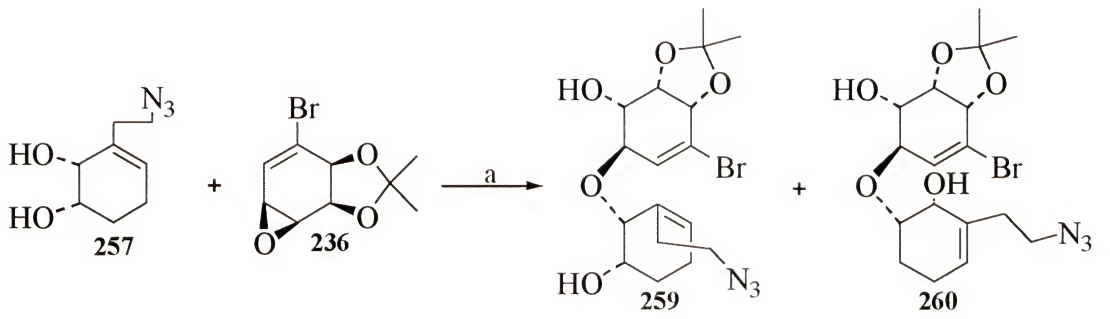
When alcohol **263** and epoxide **236** were allowed to stir at room temperature for five days in the presence of boron trifluoride etherate, desired product **264** was formed, albeit in yields lower than 10%. The use of an even smaller protecting group would have been a good idea, but in order to do so, a laborious protection-deprotection scheme would have to be developed. So, in order to circumvent this the free diol was used instead.

When diol **257** and epoxide **236** were stirred at room temperature for 5-6 days (Scheme 75), both isomers were formed in a ratio of 1:4 (**259**:**260**). The two isomers



Conditions: BF_3-Et_2O, CH_2Cl_2, room temperature, 5-6 days; b) NaH, BnBr, THF, heat.
Scheme 74

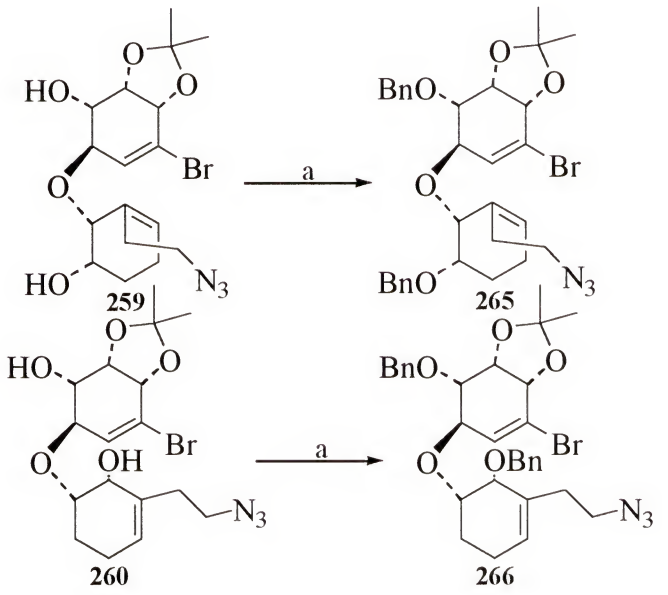
were separable by chromatography and the yields of the desired isomer ranged from 10-20%. In order to differentiate between the two isomers, both were protected as the



Conditions: a) BF_3-Et_2O, CH_2Cl_2, room temperature, 5-6 days.
Scheme 75

benzyl ethers (**265** & **266**) (Scheme 76). Their spectral properties were then compared to those of the dibenzyl ether derived from compound **264** in Scheme 74. While the

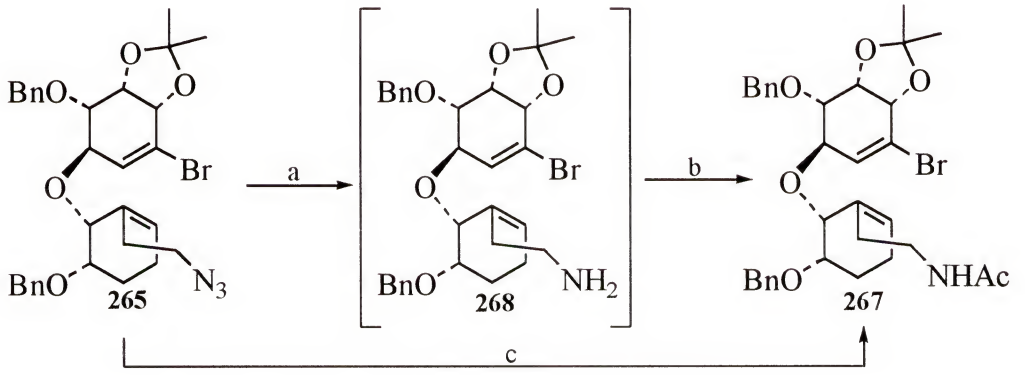
yields of the desired product (**259**) were relatively low, this method was chosen over the benzylidene route (Scheme 73 & 74) to save time and effort.



Conditions: a) NaH, BnBr, THF, heat.

Scheme 76

To avoid any undesirable side reactions during the Diels-Alder chemistry, the

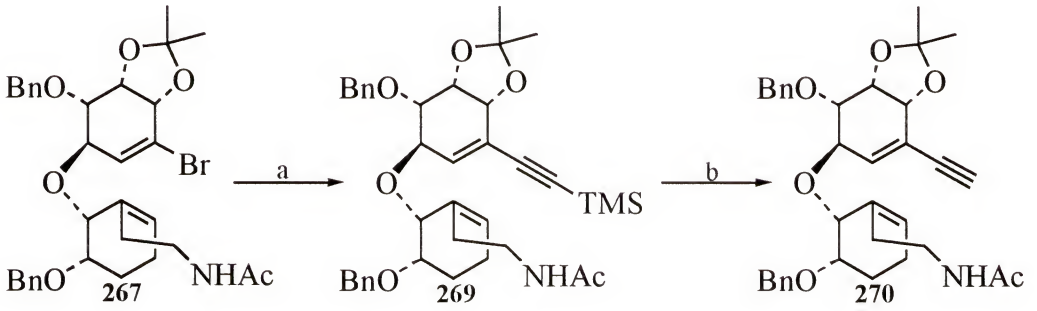


Conditions: a) PPh_3, THF, H_2O, heat; b) ClCOMe, Et_3N, CH_2Cl_2; c) CH_3COSH

Scheme 77

azide **265** was to be converted to the acetamide **267** (Scheme 77). Using Staudinger type conditions,[83] the azide **265** was heated in the presence of triphenylphosphine in THF with a trace of water to afford the amine **268** which was subsequently protected as the acetamide **267**.

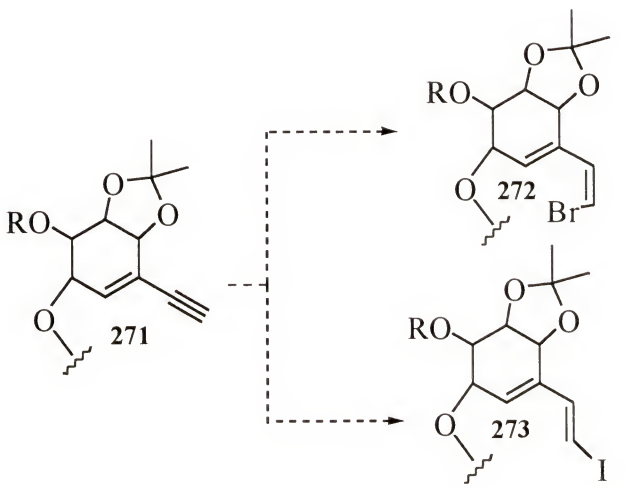
The purification of this compound proved to be difficult. The use of preparative HPLC using a reverse phase system was required to remove all of the $O=PPh_3$. An alternative to the two-step Staudinger-type reduction-acetyl protection sequence was to treat the azide **265** with thioacetic acid (Scheme 77).[84] During this reaction the azide **265** was reduced to the amine **268**, presumably via a trace of H_2S which is present to catalyze the reaction, and subsequently acetylate the nitrogen to afford **267**.



Conditions: a) TMSCCH, $PdCl_2(PPh_3)_2$, CuI, $^iPr_2NH$; b) TBAF, THF.
Scheme 78

To install the vinyl group, Sonogashira type coupling conditions[85] between the vinyl bromide **267** and trimethylsilylacetylene were used to afford **269**. Removal of the TMS group by fluoride anion afforded the enyne **270** (Scheme 78). From here on the plan was to use hydroboration chemistry developed by H.C. Brown[86] to transform the

acetylene **271** to a substituted alkene (**272** or **273**) (Scheme 79). By forming the vinyl borane first, the substituted vinyl groups could be formed stereoselectively depending on the reaction conditions. Treatment of the vinyl borane with NaOH and I_2 should give the (*E*)-iodoalkene **273** while Br_2 and NaOMe should result in the (*Z*)-bromoalkene **272**.

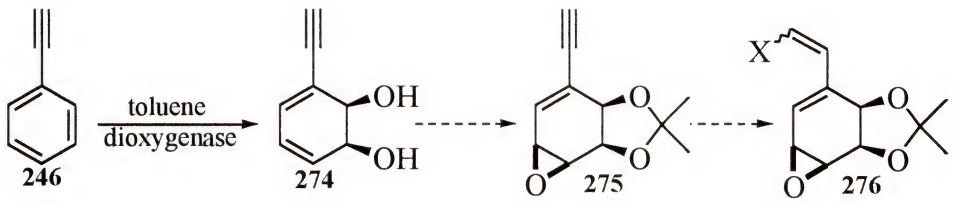


Scheme 79

While working out these conditions, an alternate and potentially better approach to the diene was being pursued and ultimately, compounds **272** and **273** were never made to complete the synthetic sequence. A combination of low yielding reactions and difficult purifications that yielded only minute quantities of the enyne **270** caused us to abandon this route. The most serious problem in this synthetic sequence was the initial coupling between epoxide **237** and diol **258**. Subsequent problems with removal of the PPh_3 and $O{=}PPh_3$ after the reduction of azide **265** (Scheme 77) were tolerable in part because of these byproduct's non participation during the Sonogashira coupling and desilyation reactions.

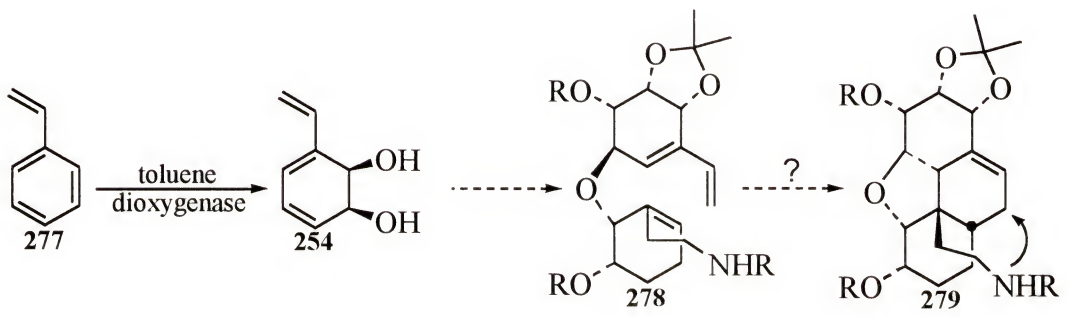
Second Synthetic Approach - β-bromostyrene as Latent Ring A

An alternative to the Sonogashira coupling reaction was envisioned in the use of the biooxidation product of phenylacetylene **274**. Phenylacetylene **246** is a known



Scheme 80

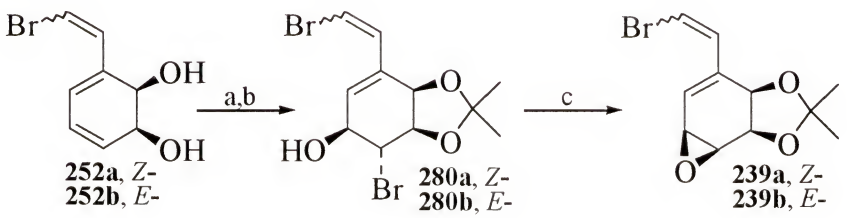
substrate for the microbial oxidation[87] and its use would eliminate the two steps needed in this synthesis to install the two carbons needed for the Diels-Alder diene (**276**) (Scheme 80). To take this a step further, styrene **277** is also a known substrate for the



Scheme 81

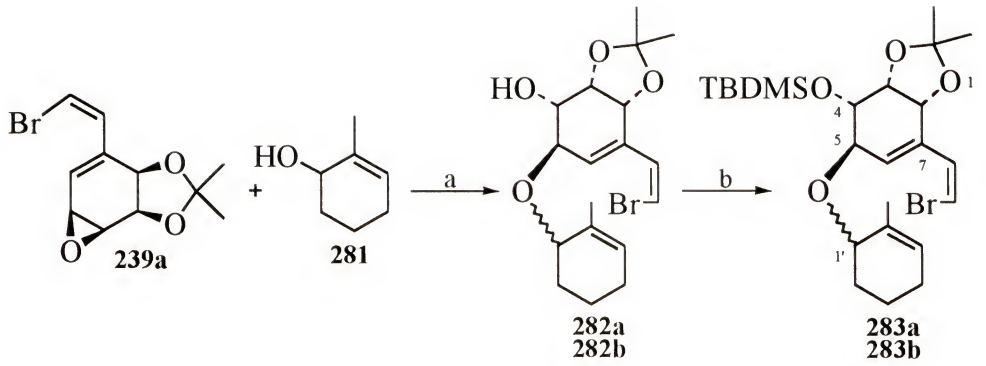
microbial oxidation (Scheme 81).[80] The vinyl group would already be in place (**278**), thereby avoiding not only the Sonogashira coupling/desilyation sequence but also the hydroboration chemistry as well. Unfortunately, there is no substitution at the β-position of the vinyl group which would become the leaving group for the substitution chemistry to form the D-ring after the Diels-Alder reaction (**279**). So, the next logical step entailed the use of β-bromostyrene **241**, a compound that has the desired substitution at the β-position of the vinyl group of styrene. The next objective was to see if β-bromostyrene (**241a** & **241b**) was also a substrate for the bacteria. In fact both (*E*)- and (*Z*)-β-bromostyrene (**241a**, **241b**) were found to be good substrates for the biooxidation process resulting in their respective diols in yields of 1 g/L of fermentation broth, as discussed in Scheme 67.

Both β-bromostyrene diols **252a** and **252b** were converted to their respective bromohydrins **280a** and **280b** and *syn* epoxides **239a** and **239b** in quantitative yields. A



Conditions: a) DMP, *p*-TsOH, CH_2Cl_2; b) DBH, acetone, H_2O; c) 10% NaOH, DME.
Scheme 83

model study was performed with the (*Z*)-bromo styrene epoxide **239a** which was coupled with alcohol **281** in the presence of boron trifluoride etherate to afford the



Conditions: a) BF_3-Et_2O, CH_2Cl_2, -78 °C; b) TBDMSCl, imidazole, DMAP, DMF.

Scheme 84

dicyclohexenyl ethers **282a** and **282b** as a diastereomeric mixture (Scheme 84). The free alcohols **282a** and **282b** were protected as the *t*-butyldimethylsilyl ethers **283a** and

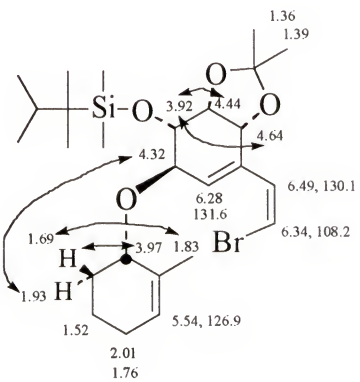
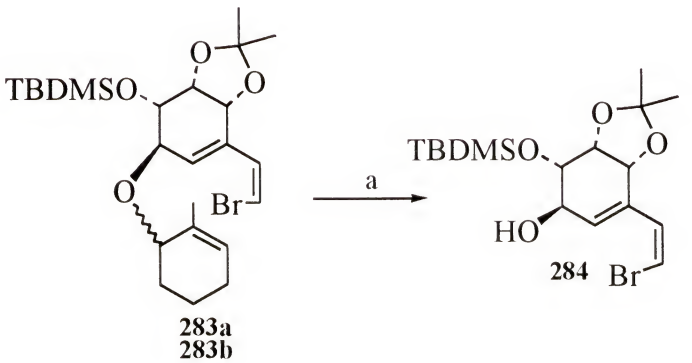


Figure 10. Stereochemical determination of triene **283a**.

283b, which were separable using preparative TLC eluting with a 1:1 mixture of methylene chloride and hexanes. The stereochemistry at C1' of isomer **283a** was

assigned using TOCSY, NOESY, and HMQC 2D experiments (Figure 10). Based on the information shown in Figure 10, it was assumed that the stereochemistry at C1' of isomer **283b** was opposite. Upon heating the trienes **283a** and **283b** in toluene at 150-



283a
283b

284

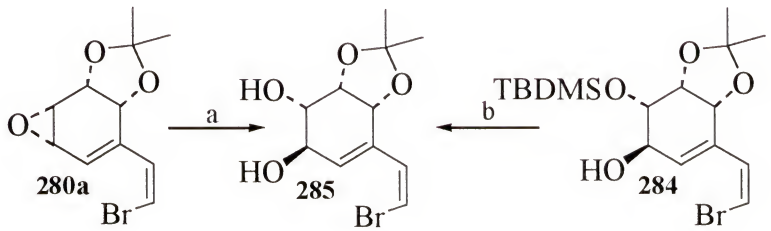
Conditions: a) 150-210 °C, PhMe, sealed tube, 3-5 days.

Scheme 85

210 °C for several days, only diene **284** was isolated (Scheme 85); it was assumed to have been formed from an elimination to the cyclohexadiene and diol. This reaction product was also formed when the sealed tube was prewashed with hexamethyldisilane or ammonium hydroxide. On the other hand, when this reaction was run in the presence of an equivalent of proton sponge no elimination products nor any new products were detected. Even after one week at temperatures above 250 °C no products were detected, only intact starting material was recovered.

To confirm the absolute stereochemistry of diene **284** a structure proof was completed (Scheme 86). Epoxide **280a** was opened under acidic conditions to give diol

285. Diene **284** was also converted to the diol **285** and the spectral data was compared to confirm the structure.



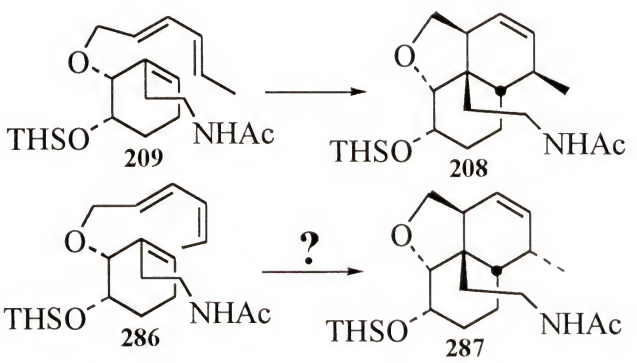
Conditions: a) 1 M H_2SO_4, DME, H_2O; b) TBAF, THF, room temperature.
Scheme 86

The results described above raised several questions that needed to be answered. The first and most critical question was whether the bromine was sterically restricting achievement of the transition state geometry needed for the IMDA reaction to occur. However, if one compares this model study with the last model study reported by Hudlicky and Gum,[66] there are three major structural differences. First, the stereochemistry of the diene has been changed from (*E,E*) to (*E,Z*). Second, the substitution of the diene's vinyl group has been changed from a methyl to a bromine. Finally, the acyclic diene has been replaced with a cyclic one. The reason that no Diels-Alder adduct was detected when triene **283** was heated in a sealed tube might therefore be a function of unfavorable steric and electronic requirement that would disfavor the Diels-Alder reaction. The cyclic nature of the diene system may restrict rotation so that the orbitals of the diene and dienophile cannot align properly for an IMDA reaction to occur. Another problem could be a result of the size of the bromine atom and the *Z*-

geometry of the vinyl group which would also discourage the proper alignment needed for an IMDA reaction to occur. Whatever the problem may be, the model system of Hudlicky and Gum required reinvestigation.

Reinvestigation of the Acyclic Model System

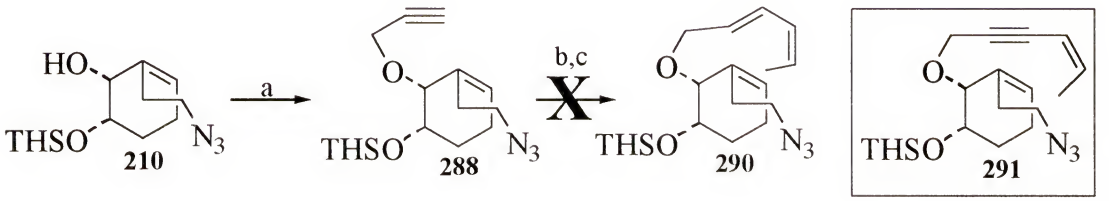
The most useful experiment to perform in order to determine whether or not the β-substituent on the vinyl group of **283** is preventing the IMDA reaction from occurring would be to construct Diels-Alder precursor (**286**), the (E,Z)-diene version of Gum's system **209** (Scheme 86). If the Diels-Alder adduct **287**, the C9 epimer of Gum's



Scheme 86

adduct **208**, were not formed from **286** then the most probable reason for the failure of the IMDA reaction would be the diene geometry. If this is the case, then this particular approach should be abandoned and more attention given to construction of a system such as that shown in Scheme 56 (**219** → **220**) where X ultimately becomes the nucleophilic nitrogen.

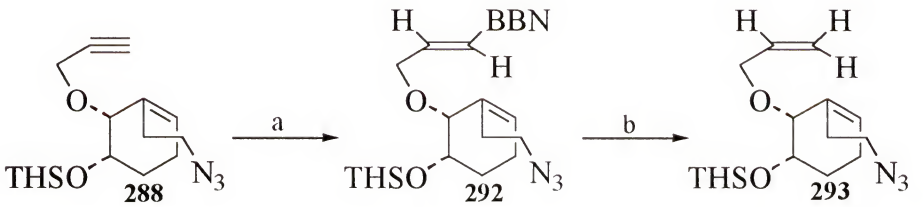
The original plan for the construction of the "(*E,Z*)-acyclic" model system was to build up the diene from the alcohol **210** used in Gum's synthesis[66] of the "(*E,E*)-acyclic" model system. Alkylation of the alcohol **210** with propargyl bromide afforded



Conditions: a) NaH, C_3H_3Br, THF; b) catechol borane, heat; c) 1-bromopropene (**289**), $Pd(Ph_3)_4$, PhH, 70 °C.

Scheme 87

the propargyl ether **288** in quantitative yield (Scheme 87). Initially the propargyl ether **288** was hydroborated with catechol borane then, using Suzuki coupling conditions,[88] the coupling of the ether with (*Z*)-1-bromopropene **289** was attempted. Unfortunately, none of the diene **290** was formed, but some of the enyne **291** was isolated, leading to the speculation that the hydroboration had not occurred. The hydroborating agent was

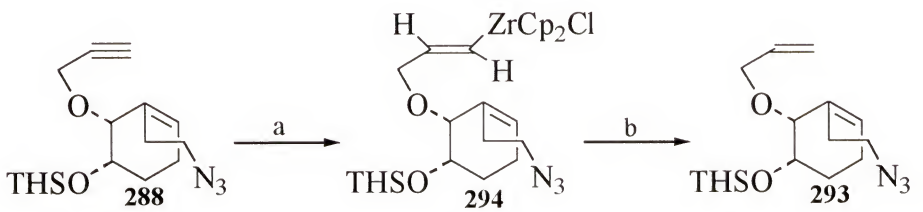


Conditions: a) 9-BBN, THF; b) AcOH.

Scheme 88

then changed to 9-borabicyclo[3.3.1]nonane and the coupling conditions were repeated. Still, no diene **290** or enyne **291** were formed. Formation of the vinyl borate **292** was assumed to occur since an acidic quench of the reaction resulted in isolation of the allyl ether **293** (Scheme 88).

An alternative coupling route was also investigated based on Whitby's work[89] with the hydrozirconation of alkynes. Treatment of propargyl ether **288** with Schwartz's reagent formed the vinyl zirconium compound **294** (Scheme 89).



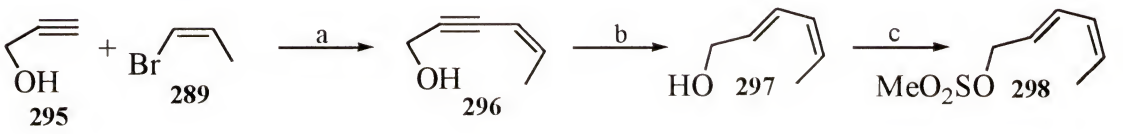
Conditions: a) $Cp_2Zr(H)Cl$, THF; b) 1-bromopropene (**289**), Pd(0) (generated by treating $Pd(Ph_3)_2Cl_2$ with 2 equivalents of EtMgBr and PPh_3), THF, overnight at room temperature or reflux then acidic work up.

Scheme 89

Compound **294** was then subjected to Negishi's coupling conditions[90] using a Pd(0) complex and (*Z*)-1-bromopropene **289**. Unfortunately, none of the diene **290** was formed, but the allylic ether **293** was isolated indicating that hydrozirconation of the propargyl ether did occur. This reaction was also repeated by generating the Pd(0) complex via Whitby's method ($Pd(Ph_3)_2Cl_2$, 2EtMgBr, $2PPh_3$)[89] and Negishi's method ($Pd(Ph_3)_2Cl_2$, 2DIBAL)[90] as well as using $Pd(Ph_3)_4$ but to no avail. It was assumed that the original conditions published by Suzuki and Negishi did not work for this model

system and significant efforts would be needed to effect the desired coupling reaction. The method was therefore abandoned in preference to another simpler route.

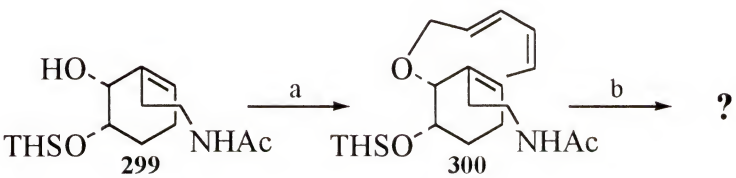
Under Sonogashira type[85] conditions, propargyl alcohol **295** and (*Z*)-1-bromopropene **289** were coupled together (Scheme 90) to give the enyne **296** in



Conditions: a) $Pd(Ph_3)_2Cl_2$, CuI, $^{i}Pr_2NH$; b) 2MeLi, 2DIBAH, DME, reflux; c) CH_3SO_2Cl, Et_3N, CH_2Cl_2.

Scheme 90

quantitative yield. The enyne **296** was then heated under reflux in anhydrous 1,2-dimethoxyethane and 2 equivalents of diisobutylmethylaluminum hydride,[91] generated in situ, to give the (*E,Z*)-diene **297**. Alcohol **297** was then treated with methanesulfonyl chloride to form the mesylate **298** which was then added to a reaction mixture of



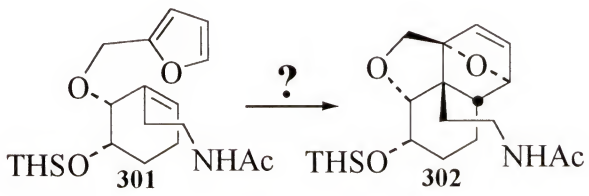
Conditions: a) NaH, **298**, THF; b) 230 °C, PhMe, sealed tube.

Scheme 91

acetamide alcohol **299**, sodium hydride and THF (Scheme 91). This was allowed to stir at room temperature overnight to afford the alkylated product **300**. Currently, triene **300** is being studied under the same conditions used with Gum's substrate **209**.[66] These results will be reported in due course.

Investigation into an Intramolecular Diels-Alder Reaction of a Furfuryl Derivative

Intramolecular Diels-Alder reactions of furans (IMDAF) have been used frequently in the synthesis of higher ordered carbocycles.[92] However, the Hudlicky group is currently the only research group that used the IMDAF reaction in the construction of precursors to morphinan skeletons.[64] Currently, a furfuryl derivative of type **301**, a natural (*E,Z*)-diene, is being investigated as to whether it will undergo IMDAF to form tricycles (**302**) similar to ones produced by Boros, Boros and Gum (Scheme 92).[63,66]

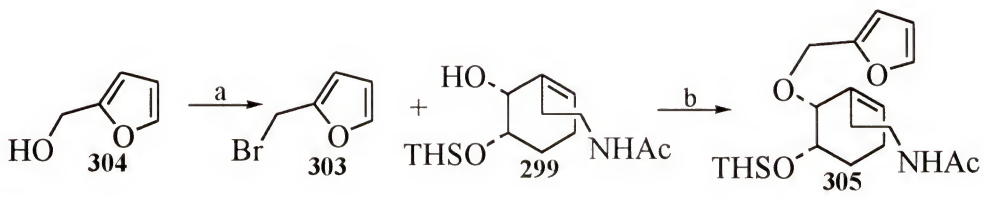


301 **302**

Scheme 92

Furfuryl bromide **303** was formed from furfuryl alcohol **304** and PBr_3 and used immediately to alkylate alcohol **299** (Scheme 93).[93] The furfuryl derivative **305** was next subjected to several different conditions used for IMDAF reactions. Thermal conditions were used first, where the derivative **305** was dissolved in toluene, placed in

a resealable tube then subjected to temperature ranges of 150-230 °C for 1 to 7 days. No Diels-Alder adducts were formed after one week under themal conditions. Only intact starting material **305** was recovered. The furfuryl derivative **305** was then treated



Conditions: a) PBr_3, Et_2O, 0 °C; b) KOH, Et_2O.

Scheme 93

with the Lewis acids $BF_3{\cdot}Et_2O$ and Et_2AlCl in CH_2Cl_2. No Diels-Alder adducts were found, only recovered starting material was isolated when Et_2AlCl was used as the Lewis acid. A small amount of the cleavage product **299** was seen after refluxing **305** in the presence of Et_2AlCl but the starting triene **305** was recovered. The use of $BF_3{\cdot}Et_2O$ caused cleavage of the ether linkage at room temperatures resulting in isolation of the starting alcohol **299**. At temperatures from -78 to 0 °C no reaction occurred but as the temperature warmed to room temperature the cleavage product **299** was formed. A reaction mixture containing furfuryl derivative **305**, cyclodextrin and H_2O was also tried for the IMDAF but it gave the same results as the Et_2AlCl and thermal conditions: no Diels-Alder adducts only recovered **305**. A reason that no IMDAF adduct is seen for **305** could be a result of the aromaticity of furan. The Diels-Alder adduct could be forming under the reaction conditions, but a retro-Diels-Adler occurs, reverting back to the more stable aromatic furan ring.

The idea of using the intramolecular Diels-Alder reaction to construct the morphinan skeleton was based on the "simple" idea of using two hydroxylated styrenes as shown in Figure 11. The stumbling blocks encountered during the investigation of

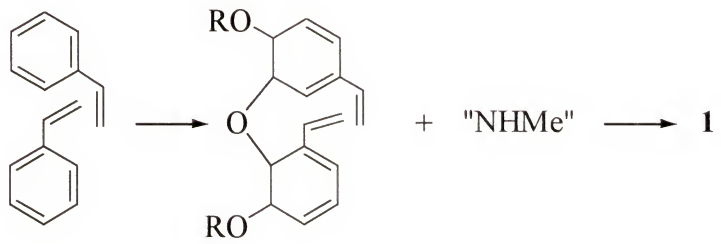


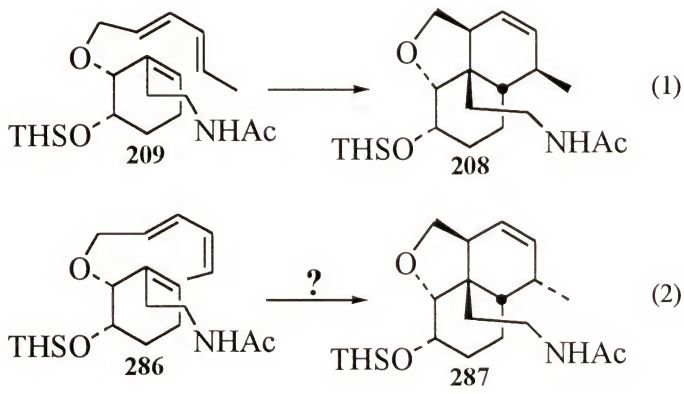
Figure 11. The morphine skeleton derived from hydroxylated styrenes.

this approach shows the difficulty of transferring a good idea into a successfully completed project. Probably the number-one difficulty always encountered in designing a synthesis was that the assumed "simple" transformations do not always turn out to be as successful in the laboratory. For example, some of these "simple" transformations that turned out to be problems during this synthesis were: (1) selective protection of the diol **257** in high yields; (2) opening of epoxide **236** with hindered alcohols; (3) conversion of an acetylene to a vinyl halide using Brown's hydroboration chemistry; (4) understanding the Diels-Alder cycloaddition (i.e., inability to form a Diels-Alder adduct of furan); and (5) difficulties in applying known reaction conditions (i.e., Suzuki, Negishi, Whitby couplings) to the synthesis of "simple" acyclic dienes. Difficulties such as these continue to bolster the reputation of the unpredictability of organic synthesis and will proceed to make this field an intellectual challenge.

CHAPTER 4
CONCLUSIONS

Summary and Conclusions

Briefly summarizing the main point of this work, a model system containing an (*E,Z*)-diene (Equation 2, Scheme 93) was needed to determine whether or not changing the geometry from an (*E,E*)-diene would result in formation of the C9 epimer of Gum's



Scheme 94

cycloaddition adduct (Equation 1, Scheme 94). The next step from Gum's model system included not only the (*E,Z*)-diene, but also a leaving group in the β-position of the vinyl group and an extra ring (**283**). The results from the Diels-Alder study showed no formation of Diels-Alder cycloadducts (Figure 12). Instead the only new product

observed was cleavage of the ether linkage resulting in the diene **284**. Reasons for no IMDA occurring could be a factor of the cyclic nature or the (*Z*)-geometry of the diene.

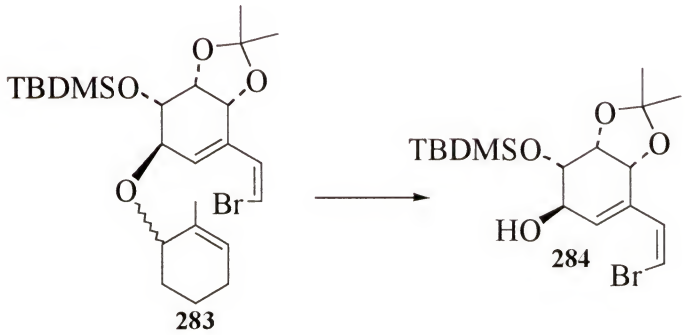


Figure 12. Elimination product of **283**.

A similar acyclic model system to Gum's containing and (*E,Z*)-diene is currently being synthesized. If no Diels-Alder adducts are seen when triene **286** is subjected to

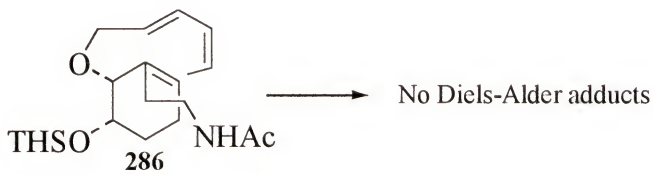


Figure 13. IMDA study of (*E,Z*)-diene system.

the same conditions as Gum's triene **209**, the (*Z*)-geometry of the diene is probably the deciding factor that blocks the formation of the IMDA transition state (Figure 13). These results would indicate that this particular approach should be abandoned, but before doing so there are a few items to consider that are stated below.

Future Ideas

One of the major problems with this particular approach is that the (*E,Z*)-diene geometry fails to produce the expected tricycle (Figure 12). The whole basis of using an (*E,Z*)-diene was to generate the C9 stereocenter as shown for tricycle **223** (Figure 14). A leaving group at this position would allow the nitrogen appendage to undergo a substitution reaction to form the D-ring of the morphinan skeleton (Figure 14).

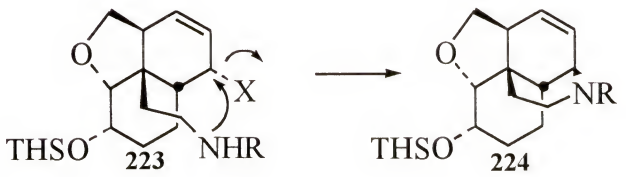


Figure 14. D-ring formation via nucleophilic substitution of N-appendage.

Since this is unattainable using the current approach the alternate approach to form the D-ring should be explored in which the nitrogen-appendage is part of the diene and the leaving group is present on the 2-carbon appendage of the dienophile (Figure 15).

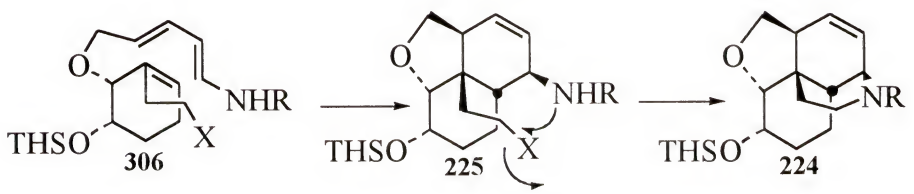
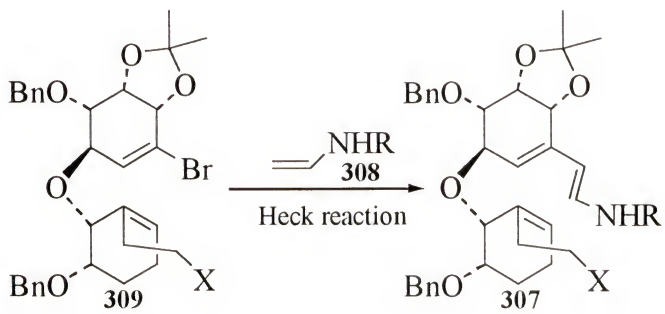


Figure 15. Alternate plan for D-ring formation.

From the Boros' and Gum's model systems, the (*E,E*)-diene undergoes IMDA to afford the stereochemistry as shown in Figure 15. By substituting a nitrogen at the C9 position, a nucleophilic sybstitution could be envisioned to take place on the 2-carbon appendage to form the D-ring.

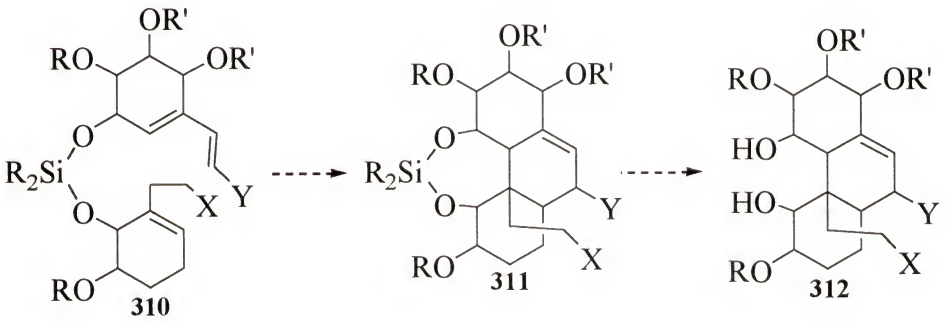
Investigation into whether or not dienes of the type **307** could be formed via the Heck reaction (Scheme 95) with vinyl amines such as **308** should be undertaken. The Hegedus[93] and Murakami[94] research groups have used methyl α-acetamidoacrylate in the Heck reaction to form tryptophan derivatives. If these dienes are easily accessible then it would be worthwhile to study the IMDA of the trienes.



Scheme 95

Another problem that needs to be addressed is the coupling between epoxide **236** and diol **257**. Currently, the Lewis acid-mediated coupling results in an extremely low yield of the desired compound. The use of a protecting group on the distal hydroxy group would be ideal. But using a large protecting group, such as the dimethylthexylsilyl chloride which is selective for the distal hydroxy group, the coupling reaction does not take place. Unfortunately, as the size of the protecting group

decreases so does the group's selectivity. A possible way around this problem is through the use of a silyl linker.[95] Craig and coworkers have studied the regio- and stereoselectivity of IMDA reactions of trienes linked together by a silyl group.[96] By linking the two "diene-diol"



Scheme 96

pieces with a silyl group, trienes of the type **310** could be formed (Scheme 96). These silyl trienes could undergo the IMDA reaction to form tetracycle **311** which upon desilylation would produce the diol **312**. This could provide enough material to at least investigate whether or not the substitution reaction between substituents Y and X (Y=Nu & X=E^+ or Y=E^+ & X=Nu) would be a feasable way to construct the D-ring of the morphinan skeleton. These two ideas represent of few relatively quick and simple experiments to determine whether or not the idea of using an intramolecular Diels-Alder reaction using the two "diene diol" pieces is a viable route to the morphinan skeleton.

CHAPTER 5
EXPERIMENTAL

General Procedures and Instrumentation

All anhydrous reactions were performed under an atmosphere of argon in solvents dried under standard procedures or purchased from Aldrich Chemical Company. Analytical TLC was performed on K6F silica gel (Whatman) plates. Preparative TLC was performed on PK6F silica gel (Whatman) plates. Flash column chromatography was performed on Fisher silica gel (grade 60, 200-425 mesh), Lagand silica gel (grade 60, 230-400 mesh) or Natland silica gel (grade 60, 200-400 mesh). The silica gel was deactivated by adding 10 mL of H_2O to every 100 g of silica gel. ^{1}H and ^{13}C NMR spectra were measured on the following Varian instruments: VXR, Gemini, or Mercury at 300 MHz in chloroform-d unless otherwise indicated using TMS as an internal standard. All 2D COESY, NOESY and TOCSY spectra were measured on a Varian Inova 500 MHz instrument. ^{13}C spectra were determined by APT, DEPT, or 2D experiments. Mass spectra were recorded on a Finnigan Mat 95 Q mass spectrometer. IR spectra were recorded on a Perkin Elmer 1600 Series instrument. Optical rotations were measured on a Perkin Elmer polarimeter. Combustion analysis were performed by Atlantic Microlab, Inc. or the University of Florida spectroscopy labs. Melting points were determined on a Unimelt apparatus and are uncorrected.

Experimental Procedures and Data

(2*S*, 3a*S*, 7a*S*)-7-(2-Azidoethyl)-2-phenyl-4,5-dihydrobenzo[d][1,3]dioxol (**261a**) and (2*R*, 3a*S*, 7a*S*)-7-(2-Azidoethyl)-2-phenyl-4,5-dihydrobenzo[d][1,3]dioxol (**261b**). (1*S*, 2*S*)-6-(2-Azidoethyl)-cyclohex-5-ene-1,2-diol (**257**) (250 mg, 1.36 mmol) was dissolved in 25 mL of CH_2Cl_2. Benzaldehyde (724 mg, 6.82 mmol) was added followed by 20 mg of *p*-toluenesulfonic acid. The reaction mixture was allowed to stir at room temperature for 60 minutes. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with 1 x 10 mL of CH_2Cl_2 and the combined organic layers were washed with 2 x 10 mL of brine. The organic extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The excess benzaldehyde was removed using a Kugelrohr distillation apparatus and the remaining residue was passed through a small plug of silica gel (3:1 hexanes:ethyl acetate) to give **261a** and **261b** (421 mg, 1.25 mmol, 92 %) as a clear yellow oil. The two diastereomers were separated using preparative HPLC eluting with a 70:30 acetonitrile:water (5 mM Et_3N-AcOH) solution as slightly yellow oils: **261a**: $R_f = 0.72$ (1:1 hexanes:ethyl acetate); $[\alpha]_D^{28} = +36.8$ (c = 0.8, $CHCl_3$); IR (neat)/cm^{-1} 2093; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.49-7.45 (m, 2H), 7.41-7.34 (m, 3H), 5.92 (t, *J* = 4.2 Hz, 1H), 5.90 (s, 1H), 4.63 (d, *J* = 5.6 Hz, 1H), 4.52 (dt, *J* = 5.5, 2.9 Hz, 1H), 3.46 (t, *J* = 6.9 Hz, 2H), 2.56-2.37 (m, 2H), 2.35-2.26 (m, 1H), 2.11-1.94 (m, 2H), 1.83-1.72 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 147.2, 138.7, 130.8, 130.2, 129.1, 128.4, 126.4, 102.2, 74.7, 74.1, 49.6, 33.7, 25.1, 20.6; HR MS (CI, CH_4): calcd for $C_{15}H_{17}O_2N_3$ + H: m/z 272.1400; found: 272.1402; Anal. calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32; found: C, 66.32; H, 6.32. **261b**: $R_f = 0.72$ (1:1 hexanes:ethyl acetate); $[\alpha]_D^{28} = -23.3$ (c = 0.85, $CHCl_3$); IR

(neat)/cm^{-1} 2096; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 7.45-7.42 (m, 2H), 7.37-7.34 (m, 3H), 5.87 (s, 1H), 5.83 (t, *J* = 4.0 Hz, 1H), 4.45 (d, *J* = 6.5 Hz, 1H), 4.38 (dt, *J* = 6.2, 4.0 Hz, 1H), 3.49-3.34 (m, 2H), 2.54-2.36 (m, 2H), 2.31-2.19 (m, 1H), 2.06-1.88 (m, 3H);^{13}C NMR ($CDCl_3$): δ 137.6, 131.9, 129.4, 128.6, 128.3, 127.0, 103.7, 74.7, 74.4, 49.6, 33.9, 25.6, 21.2; HR MS (CI, CH_4): calcd for $C_{15}H_{17}O_2N_3$ + H: m/z 272.1400; found: 272.1412; Anal. calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32; found: C, 66.43; H, 6.31.

(1*S*, 2*S*)-6-(2-Azidoethyl)-1-benzyloxy-2-hydroxycyclohex-5-ene (**263**) and (1*S*, 2*S*)-6-(2-Azidoethyl)-2-benzyloxy-1-hydroxycyclohex-5-ene (**262**).

A flame dried/argon flushed 25 mL pear-shaped flask was charged with 220 mg (0.811 mmol) of (3a*S*, 7a*S*)-7-(2-azidoethyl)-2-phenyl-4,5-dihydrobenzo[d][1,3]dioxol (**261**). Acetonitrile (5 mL) was added and the solution was cooled to 0 °C in an ice/water bath. Sodium cyanoborohydride (51 mg, 0.811 mmol) was added followed by dropwise addition of $TiCl_4$ (154 mg, 0.811 mmol). The reaction mixture was stirred at 0 °C for 15 minutes, then allowed to warm to room temperature. After 3 hours, the mixture was concentrated, then taken up in 25 mL CH_2Cl_2. The mixture was washed with 1 x 10 mL of 10 % NaOH and 1 x 10 mL brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was passed through a small pad of silica gel washing with 1:1 hexanes:ethyl acetate to give 146 mg (0.534 mmol, 66 %) of a clear oil. The mixture of isomers was separable using flash column chromatography on silica gel eluting with 1:3 hexanes:ether to give 24 mg of **263** as a clear oil. R_f = 0.69 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{30}$ = +6.63 (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3448, 2097; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 7.39-7.33 (m, 5H), 5.68 (s, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.95 (br s,

1H), 3.24 9t, J = 7.2 Hz, 2H), 2.46-2.37 (m, 1H), 2.33-2.24 (m, 2H), 2.03-1.91 (m, 3H), 1.72-1.61 (m, 1H); ^{13}C NMR ($CDCl_3$); δ 137.8, 132.0, 128.5, 128.2, 76.4, 72.5, 66.0, 49.9, 33.2, 26.3, 21.9; HR MS (FAB): calcd for $C_{15}H_{19}O_2N_3$ + H: m/z 274.1555; found: 274.1559; Anal. calcd. for $C_{15}H_{19}O_2N_3$: C, 65.91; H, 7.01; found: C, 65.69; H, 6.89. A total of 84 mg of **262** was isolated as a clear oil from the above mixture. R_f = 0.65 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{25}$ = -18.4 (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3455, 3030, 2096; ^{1}H NMR ($CDCl_3$; J/Hz): δ 7.38-7.33 (m, 5H), 5.68-5.66 (m, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.13 (d, J = 3.6 Hz, 1H), 3.63 (td, J = 9.9, 3.6 Hz, 1H), 3.45-3.40 (m, 2H), 2.55-2.46 (m, 1H), 2.24-2.33 (m, 2H), 2.27-2.29 (m, 1H), 2.07-1.96 (m, 1H), 1.95-1.83 (m, 1H), 1.79-1.70 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 138.1, 133.9, 128.5, 127.8, 127.7, 76.8, 67.0, 49.9, 34.1, 23.7, 22.1; HR MS (FAB): calcd for $C_{15}H_{19}O_2N_3$ + H: m/z 274.1528; found: 274.1559; Anal. calcd. for $C_{15}H_{19}O_2N_3$: C, 65.91; H, 7.01; found: C, 65.83; H, 7.00.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-hydroxy-5-O-[1'*S*, 2'*S*)-6'-(2-azidoethyl)-2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**264**).

A 10 mL flame dried/argon flushed pear-shaped flask was charged with 51 mg (0.187 mmol) of **263** and 69 mg (0.280 mmol) of **236**. To the reaction flask was added 500 μL of CH_2Cl_2 and the solution was cooled to 0 °C in an ice/water bath. A 1.0 M solution of BF_3-etherate (25 μL) was added to the reaction flask. The reaction mixture was stirred at 0° C until disappearance of the bromoepoxide (monitored by TLC). The reaction mixture was quenched with 2 mL of saturated $NaHCO_3$. This was stirred at room temperature for 15 minutes, then the layers were separated. The aqueous layer was extracted with 2 x 5 mL portions of CH_2Cl_2. The combined organic layers were washed

with 1 x 5 mL portions of brine, then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residual material was subjected to flash column chromatography using silica gel and eluting with 95:5 toluene:diethyl ether to give 15 mg of the coupled material. This material was subjected to column chromatography twice more, first eluting with 3:1 ether:hexanes and second with 3:2 hexanes:ethyl acetate to give 10 mg (0.0192 mmol, 10 %) of **264** as a yellow oil. R_f = 0.28 (95:5 benzene:ether); $[\alpha]_D^{25}$ = +35.6 (c = 1.05, $CHCl_3$); IR (neat)/cm^{-1} 3442, 3031, 2098; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.37-7.30 (m, 5H), 6.41 (d, *J* = 1.7 Hz, 1H), 5.69 (dd, *J* = 5.1, 1.8 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 3.81, (dd, *J* = 5.1, 1.8 Hz, 1H), 4.52-4.42 (m, 2H), 4.41 (d, *J* = 8.2 Hz, 1H), 4.22 (d, *J* = 2.5 Hz, 1H), 3.81 (dd, *J* = 8.2, 2.8 Hz, 1H), 3.61-3.55 (m, 1H), 3.45-3.40 (m, 2H), 2.63-2.58 (m, 1H), 2.47-2.37 (m, 1H), 2.32-2.26 (m, 1H), 2.11-2.02 (m, 2H), 1.95-1.87 (m, 2H), 1.39 (s, 3H), 1.28 (s, 3H); HR MS (FAB): calcd for $C_{24}H_{30}O_5N_3Br$ + H: m/z 520.1447; found: 520.1467.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-hydroxy-5-O-[(1'*S*, 2'*S*)-6'-(2-azidoethyl)-2'-hydroxycyclohex-5'-ene]cyclohex-6-ene (**259**) and (3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-hydroxy-5-O-[(1'*S*, 2'*S*)-3'-(2-azidoethyl)-2'-hydroxycyclohex-3'-ene]cyclohex-6-ene (**260**).

The procedure was run as stated above using 860 mg (4.69 mmol) of **257**, 1.74 g (7.04 mmol) of **236**, 100 μL of BF_3-etherate and 1 mL of CH_2Cl_2. (3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-hydroxy-5-O-[(1'*S*, 2'*S*)-6'-(2-azidoethyl)-2'-hydroxycyclohex-5'-ene]cyclohex-6-ene (**259**) was isolated as a brown oil (148 mg, 0.343 mmol, 7%): R_f = 0.30 (3:2 hexanes:ethyl acetate); $[\alpha]_D^{24}$ = -46.8 (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3452, 2100; ^1H NMR ($CDCl_3$; *J*/Hz): δ 6.34 (d, *J* = 1.9 Hz, 1H), 5.70 (br s, 1H), 4.62

(dd, J = 5.1, 1.8 Hz, 1H), 4.52 (dd, J = 5.1, 2.6 Hz, 1H), 4.32 (d, J = 8.2 Hz, 1H), 4.19 (s, 1H), 4.01-3.99 (m, 1H), 3.91-3.86 (m, 1H), 3.53-3.37 (m, 2H), 3.02 (d, J = 6.3 Hz, 1H), 2.62-2.53 (m, 1H), 2.43-2.24 (m, 2H), 2.11-1.88 (m, 2H), 1.71-1.63 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 132.6, 131.6, 128.7, 123.2, 110.7, 78.7, 78.5, 77.9, 76.9, 72.5, 68.0, 50.7,. 33.0, 27.4, 26.4, 26.1, 22.7; HR MS (CI): calcd for $C_{17}H_{24}O_5N_3Br$+ H: m/z 430.0978; found: 430.0946; Anal. calcd. for $C_{17}H_{24}O_5N_3Br$ + H_2O: C, 45.52; H, 5.85; N, 9.37; found: C, 45.26; H, 5.52; N, 8.39; **260** was isolated as a brown oil (573 mg, 1.33 mmol, 28%): R_f = 0.23 (3:2 hexanes:ethyl acetate); $[\alpha]_D^{25}$ = -91.8 (c = 0.85, $CHCl_3$); IR (neat)/cm^{-1} 3407, 2098; ^{1}H NMR ($CDCl_3$; J/Hz): δ 6.34 (d, J = 1.9 Hz, 1H), 5.70 (br s, 1H), 4.62 (dd, J = 5.1, 1.8 Hz, 1H), 4.52 (dd, J = 5.1, 2.6 Hz, 1H), 4.32 (d, J = 8.2 Hz, 1H), 4.19 (s, 1H), 4.01-3.99 (m, 1H), 3.91-3.86 (m, 1H), 3.53-3.37 (m, 2H), 3.02 (d, J = 6.3 Hz, 1H), 2.62-2.53 (m, 1H), 2.43-2.24 (m, 2H), 2.11-1.88 (m, 2H), 1.71-1.63 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 132.6, 131.6, 128.7, 123.2, 110.7, 78.7, 78.5, 77.9, 76.9, 72.5, 68.0, 50.7,. 33.0, 27.4, 26.4, 26.1, 22.7; HR MS (CI): calcd for $C_{17}H_{24}O_5N_3Br$+ H: m/z 430.0978; found: 430.0978; Anal. calcd. for $C_{17}H_{24}O_5N_3Br$ + 1/2H_2O: C, 46.48; H, 5.74; found: C, 46.65; H, 5.47.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-benzyloxy-5-O-[(1'*S*, 2'*S*)-6'-(2-azidoethyl)2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**265**).

A 10 mL flame dried/argon flushed pear shaped flask was charged with 10 mg of a 60 % dispersion of NaH (0.244 mmol). Diol **264** (30 mg, 0.0697 mmol) was transferred using a total of 1 mL of dry THF. After 5 minutes of stirring at room temperature, 36 mg (0.209 mmol) of benzyl bromide was added. The reaction mixture was heated under

reflux for 2 hours, cooled, and the solvent removed under reduced pressure. The remaining residue was purified by flash column chromatography using silica gel eluting with a mixture of 3:1 hexanes:ethyl acetate to give 31 mg (0.0509 mmol, 73 %) of **265** as a yellow oil. $R_f = 0.70$ (3:2 hexanes:ethyl acetate); $[\alpha]_D^{25} = -57.6$ (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3036, 3030, 2096; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.41-7.30 (m, 10H), 6.45 (d, *J* = 1.7 Hz, 1H), 5.63 (br s, 1H), 4.75-4.66 (m, 2H), 4.56-4.53 (m, 1H), 4.49-4.48 (m, 2H), 4.39 (dd, *J* = 4.7, 2.2 Hz, 1H)< 3.64 (dd, *J* = 8.5, 1.9 Hz, 1H)< 3.56-3.50 (m, 1H), 3.23, 3.14 (m, 1H), 3.10-3.02 (m, 1H), 2.49-2.24 (m, 3H), 2.09-2.00 (m, 1H), 1.94-1.85 (m, 2H), 1.30 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.2, 137.8, 134.0, 133.2, 128.9, 128.7, 128.1, 127.9, 127.4, 121.0, 110.4, 80.6, 79.0, 78.3, 78.0, 77.9, 73.6, 72.1, 70.8, 49.6, 33.4, 27.2, 26.4, 25.2, 21.3; HR MS (FAB): calcd for $C_{31}H_{36}O_5N_3Br$ + H: m/z (-N_2) 582.1857; found: 582.1891; Anal. calcd. for $C_{31}H_{36}O_5N_3Br$: C, 60.98; H, 7.23; found: C, 66.28, H, 6.17.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-benzyloxy-5-O-[(1'*S*, 2'*S*)-6'-(2-azidoethyl)-2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**265**).

The procedure was as stated above using the following quantities: **259** (220 mg, 0.511 mmol), 60 % NaH (72 mg, 1.79 mmol), BnBr (262 mg, 1.53 mmol), and THF (2 mL). The dibenzyl ether was isolated as a brown oil, 100 mg (0.164 mmol, 32%) and the spectral data matched those above.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-benzyloxy-5-O-[(1'*S*, 2'*S*)-3'-(2-azidoethyl)-2'-benzyloxycyclohex-3'-ene]cyclohex-6-ene (**266**).

The procedure was as stated above using the following quantities: **260** (603 mg, 1.40 mmol), 60 % NaH (196 mg, 4.90 mmol), BnBr (718 mg, 4.20 mmol), and THF (10

mL). The dibenzyl ether **266** was isolated as a brown oil, 500 mg (0.820 mmol, 59%): R_f = 0.69 (3:2 hexanes:ethyl acetate); $[\alpha]_D^{26}$ = -61.0 (c = 1.3, $CHCl_3$); IR (neat)/cm^{-1} 3063, 3096, 1643; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.38-7.29 (m, 10H), 6.13 (d, *J* = 1.9 Hz, 1H), 5.58 (s, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.59 (d, , *J* = 11.5 Hz, 1H), 4.52 (ddd, *J* = 13.7, 4.9, 2.0 Hz, 2H), 4.37 (d, *J* = 8.2 Hz, 1H), 3.94 (td, *J* = 11.0, 3.0 Hz, 1H), 3.57 (d, *J* = 2.7, 1H), 3.73 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.07-1.96 (m, 2H), 1.81-1.74 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$); 138.9, 137.7, 133.1, 132.4, 128.4, 128.2, 127.9, 127.8, 127.5, 127.4, 122.5, 110.6, 80.7, 79.7, 77.9, 75.1, 75.0, 74.4, 74.0, 72.6, 49.7, 33.8, 27.4, 26.4, 24.7, 22.6; HR MS (FAB): calcd for $C_{31}H_{36}O_5N_3Br$+ H: m/z 610.1918; found: 610.1857; Anal. calcd. for $C_{31}H_{36}O_5N_3Br + C_6H_{14}$: C, 63.79; H, 7.23; N, 6.03; found: C, 63.78, H, 6.46; N, 6.09.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-Bromo-2,2-dimethyl-4-benzyloxy-5-O-[(1'*S*, 2'*S*)-6'-(2-acetaminoethyl)-2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**267**).

Azide **265** (167 mg, 0.247 mmol) was dissolved in 2 mL of THF. Water (0.01 mL) followed by 108 mg (0.411 mmol) of PPh_3 was added to the reaction flask. The reaction mixture was heated under reflux for 6 hours, cooled to room temperature and the solvents evaporated under reduced pressure. The crude reaction mixture was then taken up in 5 mL of CH_2Cl_2. Triethylamine (83 mg, 0.822 mmol) was added followed by 24 mg (0.301 mmol) of acetyl chloride. This was stirred at room temperature for 30 minutes. The reaction was quenched with water and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining

residue was passed through a small pad of silica gel eluting with a 1:1 hexanes:ethyl acetate mixture to give 74 mg of a mixture of acetamide and triphenylphosphine oxide. This mixture (50 mg) was then loaded onto a preparative HPLC column eluting with 80:20 MeCN:H_2O (5 mM Et_3N-AcOH) to give 20 mg (0.0319 mmol, 13%) of the desired acetamide **267** as a brown oil: R_f = 0.20 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{25}$ = -73.2 (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3452, 1697; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.41-7.33 (m, 10H), 6.46 (d, *J* = 1.7 Hz, 1H), 5.56 (s, 1H), 5.18 (s, 1H), 4.80 (d, *J* = 12 Hz, 1H), 4.72-4.64 (m, 2H), 4.57 (d, , *J* = 8.5 Hz, 1H), 4.16 (s, 1H), 3.66 (dd, *J* = 8.8, 1.7 Hz, 1H), 3.56-3.48 (m, 1H), 3.22-3.08 (m, 2H), 2.29-2.16 (m, 3H), 1.93-1.88 (m, 2H), 1.81 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$); 169.8, 138.3, 137.9, 133.9, 128.4, 128.3, 127.9, 127.6, 127.4, 127.2, 121.1, 110.5, 80.6, 79.0, 78.5, 78.2, 78.0, 73.5, 71.6, 70.8, 38.4, 33.5, 27.3, 26.5, 25.1, 23.1, 21.3; HR MS (FAB): calcd for $C_{33}H_{40}O_6NBr$+ H: m/z 274.1555; found: 274.1559.

(3a*R*, 4*S*, 5*R*, 7a*R*)-4-benzyloxy-7-(2'-Trimethylsilylethynyl)-2,2-dimethyl-5-O-[(1'*S*, 2'*S*)-6'-(2-acetaminoethyl)-2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**269**).

A flame dried/Ar flushed flask was charged with 28 mg (0.0447 mmol) **267**. Bis-triphenylphosphine palladium (II) dichloride 6 mg (20 mol %) and 1 mg (10 mol %) of CuI was added to the flask followed by 1 mL of iPr_2NH. Trimethylsilylacetylene 9 mg (0.0894 mmol) was added to the reaction mixture and the flask was placed on a hot oil bath (50-55 °C) for 2 hours. Then 50 μL of trimethylsilylacetylene was added and the reaction mixture was heated at 50-55 °C overnight. The amine was removed under reduced pressure and the remaining residue was loaded onto a flash silica gel chromatography column and eluted with ethyl acetate. The TMS-protected enyne **269**

(23 mg, 0.0357 mmol, 80%) was isolated as a slightly brown oil. R_f = 0.75 (ethyl acetate); $[\alpha]_D^{25}$ = -69.3 (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 3418, 2147, 1655; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.46-7.30 (m, 10H), 6.41 (d, *J* = 2.2 Hz, 1H), 5.57 (br s, 1H), 5.33 (br s, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.53 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.49 (dd, *J* = 5.0, 1.8 Hz, 1H), 4.22 (d, *J* = 2.7 Hz, 1H), 3.63 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.56 (td, *J* = 10.4, 3.3 Hz, 1H), 3.22-3.10 (m, 2H), 2.34-2.17 (m, 4H), 2.12-1.90 (m, 3H), 1.83 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 0.211 (s, 9H); ^{13}C NMR ($CDCl_3$); 169.8, 139.2, 138.4, 138.0, 134.1, 128.4, 128.3, 127.9, 127.7, 127.4, 127.3, 127.2, 120.5, 110.1, 103.1, 93.9, 81.0, 78.8, 78.2, 75.5, 72.7, 71.3, 70.7, 38.6, 33.3, 27.3, 26.5, 24.9, 23.2, 21.5, -0.015; HR MS (FAB): calcd for $C_{38}H_{49}O_6NSi$ + H: m/z 644.3409; found: 644.3409.

(3a*R*, 4*S*, 5*R*, 7a*R*)-4-benzyloxy-2,2-dimethyl-7-ethynyl-5-O-[(1'*S*, 2'*S*)-6'-(2-acetaminoethyl)-2'-benzyloxycyclohex-5'-ene]cyclohex-6-ene (**270**).

A flame dried/Ar flushed flask was charged with 23 mg (0.0357 mmol) of **269**. Dry THF (0.5 mL) was added followed by a solution (0.054 mL) of 1.0 M Me_4NF in THF was added to the flask and the reaction mixture was stirred at room temperature for 20 minutes. The solvent was removed under reduced pressure and the remaining residue was loaded onto a silica gel chromatography column and eluted with ethyl acetate to give 10 mg (0.0175 mmol, 49%) of the enyne **270** as a slightly tan oil. R_f = 0.59 (ethyl acetate); $[\alpha]_D^{25}$ = -69.6 (c = 1.2, $CHCl_3$); IR (neat)/cm^{-1} 3418, 1654; ^1H NMR ($CDCl_3$; *J*/Hz): δ 7.44-7.28 (m, 10H), 6.48 (d, *J* = 2.0 Hz, 1H), 5.56 (br s, 1H), 5.23 (br s, 1H), 4.15 (d, *J* = 2.7 Hz, 1H), 3.64 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.55-3.50 (m, 1H), 3.20-3.07 (m, 2H), 2.86 (s, 1H), 2.29-2.13 (m, 4H), 2.09-2.01 (m, 1H), 1.94-1.86 (m, 2H), 1.81 (s,

3H), 1.33 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$); 169.8, 139.6, 138.4, 138.0, 134.1, 128.5, 128.3, 127.9, 127.7, 127.4, 127.3, 119.4, 110.3, 81.7, 80.8, 79.0, 78.4, 77.2, 75.5, 72.4, 71.4, 70.8, 38.5, 33.4, 27.4, 26.4, 25.1, 23.2, 21.3; HR MS (CI, CH_4): calcd for $C_{35}H_{41}O_6N$ + H: m/z 572.3012; found: 572.3021.

Dihydroxy (1*R*,2*S*)-(*Z*)-3-(2'-Bromoethylene)-3,5-cyclohexadiene (**252a**).

The whole cell fermentation was carried out as previously reported to give yields in the range of 1 g/L.[75] *Z*-β-Bromostyrene diol **252a** was isolated as a brown oil, R_f = 0.23 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{25}$ = 40.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.70 (d, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 5.6 Hz, 1H), 6.26 (d, *J* = 8.3 Hz, 1H), 6.03 (ddd, *J* = 9.6, 5.5, 2.0 Hz, 1H), 5.95 (dd, *J* = 9.4, 2.8 Hz, 1H), 4.57 (d, *J* = 6.1 Hz, 1H), 4.44-4.37 (m, 1H), 2.61 (br s, 1H), 2.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 134.3, 132.2, 130.7, 127.2, 124.0, 106.0, 69.3, 67.0.

(1*R*,2*S*)-Dihydroxy-(*E*)-3-(2'-Bromoethylene)-3,5-cyclohexadiene (**252b**).

The whole cell fermentation was carried out as previously reported to give yields in the range of 1 g/L.[75] *E*-β-Bromostyrene diol **252b** was isolated as a white solid, m.p. = 48-51 °C; R_f = 0.23 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{23}$ = 83.1 (c = 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, *J*/Hz) δ 6.76 (d, *J* = 14.0, 1H), 6.66 (d, *J* = 14.2, 1H), 6.01-5.88 (m, 3H), 4.41 (td, *J* = 5.9, 2.2, 1H), 4.25 (d, *J* = 5.9, 1H), 2.29 (br s, 1H), 1.61 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.4, 135.8, 132.2, 124.8, 124.0, 108.1, 70.0, 66.6.

(1*R*, 2*S*)-Dihydroxy-(*Z*)-3-(2'-Bromoethylene)-3-cyclohexene (**255a**) and (1*R*, 2*S*)-Dihydroxy-(*E*)-3-(2'-Bromoethylene)-3-cyclohexene (**255b**).

The crude mixture of **252a** and **252b** (2.02 g, 9.31 mmol) was dissolved in 15 mL of methanol. The reaction mixture was cooled in an ice/water bath. Potassium

diazocarboxylate (2.17 g, 11.2 mmol) was suspended in the reaction mixture. Acetic acid (3.75 mL in 5 mL of methanol) was added dropwise to the suspension. This was stirred for an hour in the ice/water bath then allowed to stir at room temperature overnight. The methanol was removed under reduced pressure and the residue was taken up in methylene chloride (45 mL) and filtered through Celite, washing the Celite with 2 x 5 mL portions of methylene chloride. The organic layer was washed with saturated sodium bicarbonate (3 x 10 mL) and brine (3 x 5 mL) then dried over magnesium sulfate. The solvent was removed under reduced pressure to give 1.32 g (6.03 mmol, 65%) of a brown residue. The two isomers were separable using flash silica gel chromatography eluting with hexanes:ethyl acetate (1:1): **255a** as a yellow oil, $R_f = 0.29$ (1:1 hexanes:ethyl acetate); $[\alpha]_D^{27} = -72.1$ (c = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.61 (d, $J = 8.1$ Hz, 1H), 6.28 (t, $J = 4.0$ Hz, 1H), 6.16 (d, $J = 8.1$ Hz, 1H), 4.53 (t, $J = 4.9$ Hz, 1H), 3.86-3.76 (m, 2H), 2.40- 2.32 (m, 2H), 1.83-1.76 (m, 2H); **255b** was isolated as a while solid, m.p. = 129-131 °C; $R_f = 0.29$ (1:1 hexanes:ethyl acetate); $[\alpha]_D^{29} = -36.4$ (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.70 (d, $J = 13.9$ Hz, 1H), 6.56 (d, $J = 13.9$ Hz, 1H), 5.87 (dd, $J = 4.9, 3.2$ Hz, 1H), 4.30 (d, $J = 3.5$ Hz, 1H), 3.79-3.73 (m, 1H), 2.35-2.16 (m, 3H), 1.79-1.72 (m, 2H), 1.67 (br s, 1H).

(3a*S*, 7a*R*)-2,2-Dimethyl-7-vinyl-4,5-dihydrobenzo[d][1,3]dioxole (**256**).

A mixture of **255a** and **255b** (1.32 g, 6.03 mmol) was dissolved in 10 mL of methylene chloride. 2,2-Dimethoxypropane (5 mL) was added to the reaction mixture followed by a catalytic amount of *p*-toluenesulfonic acid. The reaction was allowed to stir at room temperature for 30 minutes then quenched with 5 mL of saturated sodium bicarbonate. The mixture was transferred to a separatory funnel and the layers were separated. The

aqueous layer was extracted with methylene chloride (3 x 5 mL). The organic layer was washed with brine (3 x 5 mL) and then dried over magnesium sulfate. The solvent was removed under reduced pressure. The acetonide was purged with argon then 10 mL of dry THF was added. The mixture was cooled in an acetone/CO_2 bath. *t*-Butyl lithium (2.99 mL of a 1.7 M solution in pentane) was added to the reaction mixture. Once the addition was complete, the mixture was stirred for 15 minutes then quenched with methanol. The solvents were evaporated under reduced pressure. The residue was loaded onto a chromatography column of silica gel and eluted with hexanes:ethyl acetate (6:1) to give 150 mg (0.833 mmol 14%) of **256** as a clear oil, $R_f = 0.72$ (3:2 hexanes:ethyl acetate); $[\alpha]_D^{28} = 61.8$ (c = 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.33 (dd, J = 17.6, 11.0 Hz, 1H), 5.94 (t, J = 4.3 Hz, 1H), 5.41 (d, J = 17.6 Hz, 1H), 5.07 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 5.8 Hz, 1H), 4.36-4.30 (m, 1H), 2.36-2.25 (m, 1H), 2.10-1.98 (m, 1H), 1.91-1.69 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.3, 134.8, 132.1, 113.1, 108.4, 73.4, 70.9, 27.9, 26.3, 25.8, 21.6.

(3a*S*, 7a*R*)-2,2-Dimethyl-7-ethyl-4,5-dihydrobenzo[d][1,3]dioxole (**253a**).

Vinyl acetonide **256** (19 mg, 0.105 mmol) was treated with 4 equivalents of potassium diazocarboxylate and 7 equivalents of acetic acid in methanol using the same reaction conditions as stated above for the diimide reductions. The reaction was run until the starting material disappeared using TLC plates treated with a 0.1 M $AgNO_3$ solution in methanol ($R_f = 0.48$, 6:1 hexanes:ethyl acetate). The solvents from the workup were removed under reduced pressure and the residue was purified using flash column chromatography with 10% deactivated silica gel eluting with hexanes: ethyl acetate (6:1) to give 5-10 mg of **253a** as a clear oil with a very low vapor pressure. In order to

reduce the risk of losing product, the deprotection was done during the workup to give the diol (see experimental for (1*R*,2*S*)-Dihydroxy-3-ethyl-3-cyclohexene): ^{1}H NMR ($CHCl_3$, *J*/Hz) δ 5.59 (br s, 1H), 4.38-4.36 (m, 1H), 4.32-4.27 (m, 1H), 2.23-2.04 (m, 3H), 1.94-1.67 (m, 3H), 1.39 (s, 6H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CHCl_3$) δ 123.4, 108.2, 73.9, 73.6, 27.9, 26.5, 26.4, 25.7, 20.8, 12.0, 9.30.

(1*R*,2*S*)-Dihydroxy-3-ethyl-3-cyclohexene (**253**).

Styrene diol **254** (213 mg, 1.54 mmol) was dissolved in 8 mL of methanol. The mixture was cooled in an ice/water bath. Potassium diazocarboxylate (1.05 mg, 5.40 mmol) was added. Acetic acid (0.617 mL in 2 mL of methanol) was added to the suspension. The reaction mixture was stirred in the cold bath for 30 minutes then allowed to stir at room temperature overnight. The solvents were evaporated under reduced pressure. The residue was taken up in 15 mL of methylene chloride and filtered through Celite. The Celite was washed with 2 x 5 mL portions of methylene chloride. The organic layer was washed with saturated sodium bicarbonate (3 x 5 mL) and brine (3 x 5 mL) then dried over magnesium bicarbonate. The solvent was evaporated under reduced pressure to give 150 mg (1.05 mmol, 68%) of **253** as a white solid, m.p. = 79-80 °C; R_f = 0.12 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{27}$ = -150.2 (c = 1.0 , $CHCl_3$); IR (KBR/cm^{-1}) ν 3275, 1459; ^{1}H NMR ($CHCl_3$, *J*/Hz) δ 5.54 (br s, 1H), 3.98 (d J = 3.8 Hz, 1H), 3.75 – 3.69 (m, 1H), 2.77 (br s, 2H), 2.21 – 2.05 9m, 4H), 1.73 – 1.65 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CHCl_3$) δ 139.1, 123.7, 69.8, 68.8, 27.1, 25.3, 24.0, 12.4; HRMS (EI): calcd for $C_8H_{15}O_2$: m/z 143.1776; found: 143.1072; Anal. calcd. for $C_8H_{14}O_2$ +1/3H_2O: C, 65.10; H, 9.97; found: C, 65.21; H, 9.56; Also, the acetonide **256** (25 mg) was treated with 4 equivalents of potassium diazocarboxylate and 7 equivalents of

acetic acid in methanol using the same reaction conditions as stated above for the diimide reductions. Once the potassium acetate was removed using Celite, methanol was added to the mixture of acetonide and methylene chloride followed by several drops of concentrated HCl. The reaction was run until the disappearance of starting material was seen via TLC (1:1 hexanes:ethyl acetate). The solvents were removed under reduced pressure and the residue was purified using flash column chromatography with 10% deactivated silica gel eluting with hexanes: ethyl acetate (1:1) to give **253** as a white solid: m.p. 78-79 °C; $[\alpha]_D^{25}$ = -156.9 (c = 1.0 , $CHCl_3$).

(3a*R*, 4*R*, 5*R*, 7a*S*)-4-Bromo-7-(2'-Bromo-(*Z*)-ethylene)-2,2-dimethyl-4,5-dihydrobenzo[d][1,3]dioxol-5-ol (**280a**) and (3a*R*, 4*R*, 5*R*, 7a*S*)-4-Bromo-7-(2'-Bromo-(*E*)-ethylene)-2,2-dimethyl-4,5-dihydrobenzo[d][1,3]dioxol-5-ol (**280b**).

A crude mixture of 1.5 g (6.91 mmol) of *Z*- and *E*-β-bromostyrene diols **252a** and **252b** was protected as the acetonide as stated above and purified using flash column chromatography (10% deactivated silica gel) by eluting with hexanes:ethyl acetate (6:1) to give 956 mg (3.72 mmol) of the acetonide as a yellow oil. This was taken up in 10 mL of acetone. Water (1 mL) was added and the mixture was cooled in an ice/water bath. 1,3-Dibromo-5,5-dimethylhydantoin (532 mg, 1.86 mmol) was added and the mixture was stirred for 2 hours. The reaction was quenched with 10 mL of 10% Na_2SO_3. The acetone was removed under reduced pressure. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The organic layer was washed with brine (3 x 5 mL), dried over magnesium sulfate and partially purified via flash chromatography using 10% deactivated silica gel eluting with a 6:1 hexanes:ethyl acetate mixture. The mixture of isomers was separated using a semi-preparatory HPLC

column (Primesphere C-18) eluting with 50:50 MeCN:H_2O, 5 mmol Et_3N:HOAc at a rate of 5 mL/min to give both isomers as white solids: *Z*-bromohydrin **280a**: m.p. = 94-96 °C; R_f = 0.27 (6:1 hexanes:ethyl acetate); $[\alpha]_D^{26}$ = -43.5 (c = 0.95, $CHCl_3$) ^1H NMR ($CDCl_3$) δ 6.62 (dd, *J* = 8.3, 0.5 Hz, 1H), 6.44-6.41 (m, 2H), 4.87 (d, *J* = 5.6 Hz, 1H), 4.50 (dd, *J* = 8.1, 5.6 Hz, 1H), 4.39 (dt, *J* = 1.5 Hz, 1H), 4.11 (dd, *J* = 8.1, 7.8Hz, 1H), 2.71 (d, *J* = 6.4 Hz, 1H), 1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CHCl_3$) δ 132.0, 131.4, 129.6, 111.2, 108.8, 77.5, 73.4, 70.3, 54.7, 28.2, 26.0; IR (KBR/cm^{-1}) ν 3404; HRMS (CI): calcd for $C_{11}H_{15}O_3Br_2$: m/z 352.9231; found: 352.9376; Anal. calcd. for $C_{11}H_{14}O_3Br_2$: C, 37.32; H, 3.99; found: C, 37.54; H, 3.97; *E*-bromohydrin **280b**: m.p. = 128-130 °C; R_f = 0.23 (6:1 hexanes:ethyl acetate); $[\alpha]_D^{26}$ = 22.3 (c = 1.0, $CHCl_3$) ^1H NMR ($CDCl_3$) δ 6.75 (d, *J* = 14.1 Hz, 1H), 6.69 (d, *J* = 14.1 Hz, 1H), 5.92 (d, *J* = 2.9 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.48 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.33 (dt, *J* = 6.8, 3.0 Hz, 1H), 4.06 (dd, *J* = 8.3, 7.8 Hz, 1H), 2.66 (d, *J* = 6.1 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CHCl_3$) δ 135.7, 133.0, 130.8, 111.4, 110.7, 77.7, 71.9, 70.3, 55.0, 28.1, 26.2; IR (KBR/cm^{-1}) ν 3387; HRMS (CI): calcd for $C_{11}H_{15}O_3Br_2$: m/z 352.9231; found: 352.9279; Anal. calcd. for $C_8H_{14}O_2$ +1/3H_2O: C, 65.10; H, 9.97; found: C, 36.72; H, 3.95.

(3a*R*, 4*S*, 5*S*, 7a*S*)-7-(2'-Bromo-(*Z*)-ethylene)-4,5-epoxy-2,2-dimethyl-4,5-dihydrobenzo[d][1,3]dioxole (**239a**) and (3a*R*, 4*S*, 5*S*, 7a*S*)-7-(2'-Bromo-(*E*)-ethylene)-4,5-epoxy-2,2-dimethyl-4,5-dihydrobenzo[d][1,3]dioxole (**239b**).

Epoxide **239a**: A flame dried/argon flushed flask was charged with 1.86 g (5.25 mmol) of sodium hydride. The NaH was suspended in 5 mL of dry THF and cooled in an ice/water bath. The *Z*-bromohydrin **280a** was added in a solution of dry THF (5 mL)

dropwise to the suspension of NaH. The reaction mixture was stirred in the cold bath for 1 hour, then allowed to warm up to room temperature and stir for 2 hours. The reaction was quenched with 10 mL of water, the layers separated, and the aqueous layer extracted with ether (3 x 10 mL). The ether layers were washed with brine (3 x 5 mL) and dried over magnesium sulfate. The product was purified using flash column chromatography (10% deactivated silica gel) eluting with hexanes:ethyl acetate (5:1) to give 507 mg (1.86 mmol, 35%) of **239a** as a white solid: m.p. = 90-92 °C; R_f = 0.23 (6:1 hexanes:ethyl acetate); $[\alpha]_D^{28}$ = -96.5 (c = 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 6.97 (d, *J* = 4.2 Hz, 1H), 6.63 (dd, *J* = 8.3, 0.73 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 1H), 4.90 (dd, *J* = 6.5, 1.8 Hz, 1H), 4.48 (dd, *J* = 6.3, 2.4 Hz, 1H), 3.68 (p, *J* = 2.1 Hz, 1H), 3.57 (t, *J* = 4.2 Hz, 1H), 1.56 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CHCl_3$) δ 136.2, 130.9, 129.9, 108.3, 107.9, 73.3, 71.8, 56.0, 49.7, 27.5, 25.3; IR (KBR/cm^{-1}) ν 1628; HRMS (CI): calcd for $C_{11}H_{14}O_3Br$: m/z 273.0126; found: 273.0199; Anal. calcd. for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80; found: C, 48.53; H, 4.88; Epoxide **239b**: Procedure same as for *Z*-Bromoepoxide **239a** using 69 mg (0.195 mmol) of the *E*-bromohydrin **280b** and 8 mg (0.195 mmol) of NaH to give 20 mg (0.0733 mmol, 38%) of **239b** as a white solid: R_f = 0.19 (6:1 hexanes:ethyl acetate); $[\alpha]_D^{27}$ = -48.1 (c = 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 6.80 (d, *J* = 13.9 Hz, 1H), 6.63 (dd, *J* = 13.9, 0.73 Hz, 1H), 6.23 (dd, *J* = 3.8, 0.74 Hz, 1H), 4.70 (dd, *J* = 6.6, 1.7 Hz, 1H), 4.48 (dd, *J* = 6.7, 2.6 Hz, 1H), 3.68-3.65 (m, 1H), 3.54 (t, *J* = 4.1 Hz, 1H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CHCl_3$) δ 137.3, 136.7, 127.3, 110.3, 108.6, 73.3, 69.3, 55.1, 49.7, 27.3, 25.4; HRMS (CI): calcd for $C_{11}H_{14}O_3Br$: m/z 273.0126; found: 273.0157; Anal. calcd. for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80; found: C, 47.98; H, 4.73.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-(*Z*-2'-Bromoethene)-2,2-dimethyl-4-*tert*-butyldimethylsilyloxy-5-O-[(1'*S*)-6'-methylcyclohex-5'-ene]cyclohex-6-ene (**283a**) and (3a*R*, 4*S*, 5*R*, 7a*R*)-7-(*Z*-2'-Bromoethene)-2,2-dimethyl-4-*tert*-butyldimethylsilyloxy-5-O-[(1'*R*)-6'-methylcyclohex-5'-ene]cyclohex-6-ene (**283b**).

A flame dried/Ar flushed pearshaped flask was charged with 1.35 g (4.87 mmol) of *Z*-β-bromostyrene epoxide **239a**. 1-Hydroxy-2-methylcyclohex-2-ene (**281**) (818 mg, 7.29 mmol) was added to the flask followed by 5 mL of dry CH_2Cl_2. The reaction flask was cooled to -78 °C in a dry ice/isopropanol bath. Boron trifluoride etherate (0.185 mL, 1.46 mmol) was added to the reaction flask and the mixture was stirred in the cold bath for 1 hour. The reaction was quenched with 5 mL of water and warmed to room temperature. The layers were separated and the aqueous layer was extracted with 3 x 10 mL portions of CH_2Cl_2. The organic layer was washed with 3 x 10 mL portions of brine and dried over $MgSO_4$. The solid was filtered and the solvent removed under reduced pressure. The residue was run through a short pad of 10 % deactivated silica gel to give 206 mg (0.535 mmol, 11%) of the diastereomeric isomers **282a** and **282b** as an oil (R_f = 0.30, 2:1 hexanes:ethyl acetate);. These isomers were dried overnight under high vacuum. The diastereomeric isomers **282a** and **282b** were flushed with Ar and 3 mL of anhydrous DMF was added. Imidazole (109 mg, 1.60 mmol) was added followed by 242 mg (1.60 mmol) of *tert*-butyldimethylsilyl chloride and 39 mg (0.321 mmol) of DMAP. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 10 mL of water and extracted with 3 x 20 mL portions of ether. The ether layers were washed with 3 x 10 mL portions of brine and dried over $MgSO_4$. The solid was filtered and the solvents were removed under reduced pressure.

The remaining material was purified using flash column chromatography (10% deactivated silica gel) eluting with a hexanes:ethyl acetate (1:1) mixture to give approximately 150 mg of a clear oil. The two diastereoismers **283a** and **283b** were separated using preparatory TLC eluting with a CH_2Cl_2:hexanes (1:1) mixture to give 73 mg of **283a** and 52 mg of **283b** as clear oils: Data for **283a**: $R_f = 0.75$ (2:1 hexanes:ethyl acetate); $[\alpha]_D^{29} = -81.8$ (c = 1.1, $CHCl_3$); IR (neat)/cm^{-1} 1646; ^1H NMR ($CDCl_3$; *J*/Hz): δ 6.49 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 8.1 Hz, 1H), 6.27 (br s, 1H), 5.54 (br s, 1H), 4.64 (dd, *J* = 4.9, 2.0 Hz, 1H), 4.44 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.31 (d, *J* = 8.1 Hz, 1H), 3.97 (br s, 1H), 3.92 (dd, *J* = 7.8, 2.4 Hz, 1H), 2.07-1.88 (m, 2H), 1.82 (d, *J* = 1.7 Hz, 3H), 1.79-1.67 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 0.944 (s, 9H), 0.156 (s, 6H); ^{13}C NMR ($CDCl_3$); 134.3, 131.6, 131.5, 129.9, 125.9, 109.7, 107.9, 77.3, 76.4, 75.4, 75.2, 73.2, 29.0, 27.7, 26.5, 26.1, 25.5, 21.8, 18.5, 17.9, -3.89, -4.40; HR MS (CI, CH_4): calcd for $C_{24}H_{39}O_4SiBr$ + H: m/z 499.1879; found: 499.1830; Data for **283b**: $R_f = 0.75$ (1:1 hexanes:ethyl acetate); $[\alpha]_D^{29} = -45.8$ (c = 1.8, $CHCl_3$); IR (neat)/cm^{-1} 1646; ^1H NMR ($CDCl_3$; *J*/Hz): δ 6.53 (d, *J* = 8.1 Hz, 1H), 6.38 (br s, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 5.58 (br s, 1H), 4.60 (dd, *J* = 4.9, 2.0 Hz, 1H), 4.43 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.23 (d, *J* = 8.3 Hz, 1H), 3.82 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.77 (br s, 1H), 2.08-1.81 (m, 3H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.74-1.46 (m, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 0.939 (s, 9H), 0.144 (s, 6H); ^{13}C NMR ($CDCl_3$); 133.9, 131.6, 130.3, 130.1, 126.6, 110.0, 108.1, 77.8, 75.9, 75.0, 74.9, 72.6, 28.0, 27.9, 26.8, 26.2, 25.8, 21.8, 18.8, 18.8, 18.7, -3.76, -4.57; HR MS (CI, CH_4): calcd for $C_{24}H_{39}O_4SiBr$ + H: m/z 499.1879; found: after several submissions, no m/z at 499, but repeatedly see m/z at 405 and 391 (-TBS or C_7H_{10}).

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-(*Z*-2'-Bromoethene)-4-*tert*-butyldimethylsilyloxy-2,2-dimethyl-5-hydroxycyclohex-6-ene (**284**).

Ammonium hydroxide (15 mL) was added to a thick walled resealable tube and placed in a preheated sand bath (150-155 °C) for 30 minutes. The base was decanted and a septum was placed on the tube and attached to a high vacuum line. The tube was flame dried under vacuum and cooled under Ar. The triene (**283a**, **283b** or a mixture of **283a** and **283b**) (14 mg, 0.0286 mmol) was transferred to the tube in 1-2 mL portions of dry toluene (7 mL total). The reaction mixture was degassed for 15 minutes then underwent the freeze-pump-thaw method to remove any trapped gases from the solvent. Once the tube was at room temperature under a positive pressure of Ar, the cap was sealed and the tube was buried in the preheated sand bath (150-155 °C) for 24 hours. Reaction times varied from 24 hours to 5 days. TLC samples were taken periodically (7:1 hexanes:ethyl acetate) by first allowing the reaction tube to cool to room temperature and then degassing the reaction mixture for 15 minutes after taking the sample but before placing the tube back into the sand bath. Upon completion of the reaction, the tube was cooled to room temperature and the toluene was removed under reduced pressure. The remaining residue was subjected to silica gel column chromatography, eluting with a hexane:ethyl acetate (7:1) mixture to give 6 mg (0.0148 mmol, 52%) of diene **284** as a clear oil. $R_f = 0.20$ (7:1 hexanes:ethyl acetate); $[\alpha]_D^{29} = 7.63$ (c = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$; *J*/Hz): δ 6.64 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 1H), 6.19 (d, *J* = 2.9 Hz, 1H), 4.71 (d, *J* = 6.4 Hz, 1H), 4.37-4.34 (m, 2H), 3.88 (td, *J* = 5.9, 3.7 Hz, 1H), 2.61 (d, *J* = 6.1 Hz, 1H), 1.51 (s, 3H), 1.41 (m, 3H), 0.914 (s, 9H), 0.131 (s, 6H); ^{13}C NMR ($CDCl_3$); 131.7, 131.5, 130.1, 110.7, 77.2, 74.8, 72.3, 67.8, 67.4,

26.8, 25.9, 25.7, 18.1, -0.015, -4.57, -4.88; ; HR MS (CI): calcd for $C_{17}H_{29}O_4SiBr$ + H: m/z 405.1109; found: 405.1041.

(3a*R*, 4*S*, 5*R*, 7a*R*)-7-(*Z*-2'-Bromoethene)-2,2-dimethyl-4,5-dihydroxycyclohex-6-ene (**285**).

Z-β-Bromostyrene epoxide **280a** (151 mg, 0.553 mmol) was dissolved in 10 mL of 1,2-dimethoxyethane. Deionized water (3 mL) was added and the reaction mixture was cooled in an ice/water bath. A few drops of 1 M H_2SO_4 was added to the reaction flask and the mixture was stirred in the cold bath overnight, allowing the bath to warm up to room temperature. The DME was removed under reduced pressure and 5 mL of H_2O was added to the flask. The aqueous layer was extracted with 3 x 15 mL portions of ethyl acetate. The organic layers were washed with 3 x 10 mL portions of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining residue was loaded onto a chromatographic column of silica gel and eluted with ethyl acetate to give 60 mg (0.206 mmol, 37%) of **285** as a white solid, mp = 132-133 °C (recrystallized from CH_2Cl_2/hexanes); R_f = 0.20 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{29}$ = -24.5 (c = 1.1, $CHCl_3$); IR (KBr)/cm^{-1} 3386; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 6.52 (d, *J* = 8.1 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 6.28 (s, 1H), 4.78 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.57 (dd, *J* = 5.4, 2.9 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 3.69 (dt, *J* = 7.8, 2.4 Hz, 1H), 2.95 (d, *J* = 6.8 Hz, 1H), 2.82 (d, *J* = 4.4 Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$); 132.3, 131.4, 129.8, 110.2, 108.7, 75.7, 75.6, 73.8, 69.0, 27.3, 26.3; HR MS (CI): calcd for $C_{11}H_{15}O_4Br$ + H: m/z 291.0232; found: 291.0228; Anal. calcd. for $C_{11}H_{15}O_4Br$: C, 45.38; H, 5.19; found: C, 45.77; H, 5.33.

(1*S*, 2*S*)-6-(2-Azidoethyl)-2-dimethylthexylsilyloxy-1-prop-2'-ynyloxycyclohex-5-ene (**288**).

A flame dried/Ar flushed pear-shaped flask was charged with 21 mg (0.528 mmol) of NaH. THF (2.0 mL) was added to this flask followed by addition of 86 mg (0.264 mmol) of (1*S*, 2*S*)-6-(2-azidoethyl)-2-dimethylthexylsilyloxy-1-hydroxycyclohex-5-ene **210** in 1.0 mL of THF. After stirring at room temperature for 10 minutes, 79 mg (0.528 mmol) of propargyl bromide was added and the reaction mixture was allowed to stir at room temperature overnight. The mixture was then quenched with H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (3 x 10 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The propargyl ether was then purified via flash column chromatography using 10% deactivated silica gel to give 61 mg (0.168 mmol, 63%) of **288** as a yellow oil. R_f = 0.70 (4:1 hexanes:ethyl acetate); $[\alpha]_D^{25}$ = -35.6 (c = 1.05, $CHCl_3$); IR (neat)/cm^{-1} 2096; ^1H NMR ($CDCl_3$; *J*/Hz): δ 5.79 (s, 1H), 4.74 (dd, *J* = 16.1, 2.3 Hz, 1H), 4.61 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.09 (s, 1H), 4.03 (td, , *J* = 11.3, 3.2 Hz, 1H), 3.67-3.49 (m, 2H), 2.68-2.50 (m, 3H), 2.40-2.34 (m, 1H), 2.27-2.22 (m, 1H), 2.16-2.01 (m, 1H), 1.88-1.74 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 1.05 (s, 6H), 0.323 (s, 6H); ^{13}C NMR ($CDCl_3$); 132.9, 128.1, 80.9, 75.3, 74.2, 72.3, 59.0, 50.1, 34.0, 33.9, 25.3, 24.9, 24.8, 20.2, 20.1, 18.5, 18.4, -2.69, -2.75; HR MS (FAB): calcd for $C_{19}H_{33}O_2N_3Si$+ H: m/z 364.2420; found: 364.2434; Anal. calcd. for $C_{19}H_{33}O_2N_3Si$: C, 62.77; H, 9.15; found: C, 66.09; H, 9.82.

(1*S*, 2*S*)-6-(2-Azidoethyl)-2-dimethylthexylsilyloxy-1-*Z*-hex-4'-en-2'-ynyloxycyclohex-5-ene (**291**).

Propargyl ether **288** (367 mg, 1.01 mmol) was dissolved in 2.0 mL of $^{i}Pr_2NH$. Bisdiphenylphosphinedichloropalladium (II) (71 mg, 10 mol%) and CuI (2 mg, 1 mol% mmol) were added to the mixture followed by 305 mg (2.52 mmol) of 1-bromopropene. The reaction mixture was heated between 50 and 60 °C overnight. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The remaining residue was loaded onto a column of 10% deactivated silica gel and eluted with 3:1 mixture of hexanes:ethyl acetate to give 50 mg (0.124 mmol, 12%) of **291** as a yellow oil. $R_f = 0.71$ (4:1 hexanes:ethyl acetate); $[\alpha]_D^{27} = -24.6$ (c = 1.0, $CHCl_3$); IR (neat)/cm^{-1} 2096; ^1H NMR ($CDCl_3$; *J*/Hz): δ 5.99 (dq, *J* = 10.7, 6.8 Hz, 1H), 5.58 (s, 1H), 5.51 (dq, *J* = 10.8, 1.7 Hz, 1H), 4.69 (dd, *J* = 16.0, 2.0 Hz, 1H), 4.57 (dd, *J* = 16.0, 1.8 Hz, 1H), 3.93 (d, *J* = 2.8 Hz, 1H), 3.83 (td, , *J* = 11.3, 3.2 Hz, 1H), 3.44 (dt, *J* = 11.5, 3.2 Hz, 1H), 3.35 (ddd, *J* = 12.4, 7.4, 6.1 Hz, 1H), 2.46 (dt, *J* = 14.6, 7.0 Hz, 1H), 2.37 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.20-2.14 (m, 1H), 2.04-2.02 (m, 1H), 1.96-1.90 (m, 1H), 1.89 (dd, *J* = 7.0, 1.9 Hz, 3H), 1.78-1.76 (m, 1H), 1.68-1.56 (m, 3H), 0.889 (s, 3H), 0.867 (s, 3H), 0.845 (s, 6H), 0.120 (s, 6H); ^{13}C NMR ($CDCl_3$); 139.0, 133.2, 128.0, 112.1, 109.5, 90.8, 75.0, 72.4, 59.9, 50.2, 34.1, 34.0, 25.5, 25.0, 20.3, 18.6, 16.0, -2.55; HR MS (FAB): calcd for $C_{22}H_{37}O_2N_3Si$+ H: m/z (-Me) 391.2655; found: 391.2682.

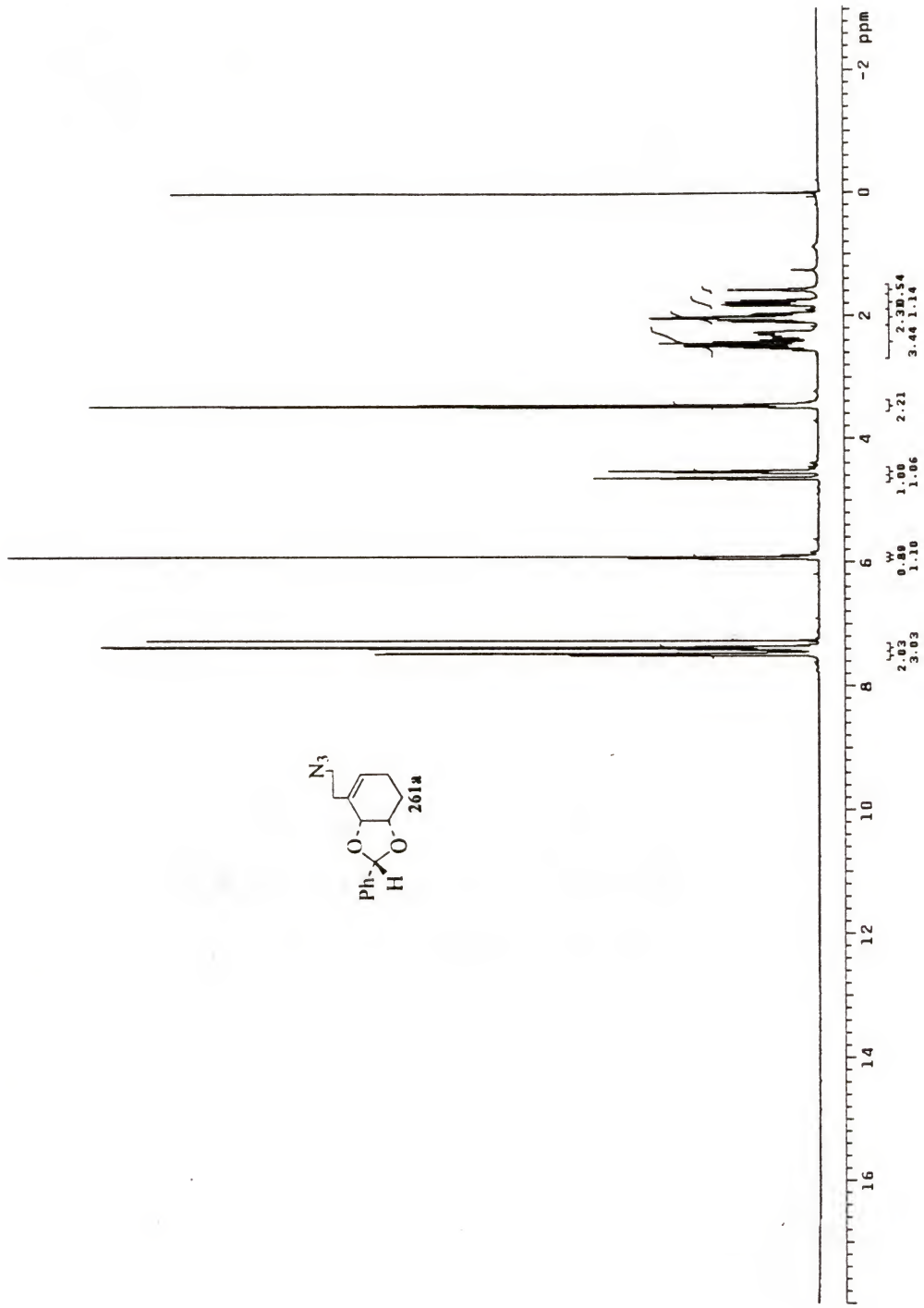
(1*S*, 2*S*)-6-(2-Azidoethyl)-2-dimethylthexylsilyloxy-1-prop-2'-enyloxycyclohex-5-ene **(293)**.

A flame dried/Ar flushed flask was charged with 100 mg (0.275 mmol) **211**. To the flask was added 0.550 mL of a 0.5 M solution of 9-BBN in THF. This reaction mixture was stirred at room temperature for 2 hours then quenced with 5 mL of 6N HCl. The

mixture was stirred at room temperature for 1 hour then extracted with ethyl acetate (3 x 10 mL). The organic layers were washed with (2 x 5 mL) brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 52 mg (0.146 mmol, 53%) of **293** as a sighltly yellow oil. $R_f = 0.71$ (4:1 hexanes:ethyl acetate); $[\alpha]_D^{27} = -45.6$ (c = 1.1, $CHCl_3$); IR (neat)/cm^{-1} 2097; ^1H NMR ($CDCl_3$; *J*/Hz): δ 5.94 (dddd, *J* = 17.1, 10.3, 6.6, 5.3 Hz, 1H), 5.55 (d, *J* = 4.1 Hz, 1H), 5.24 (qd, *J* = 17.2, 1.6 Hz, 1H), 5.15 (qd, *J* = 10.3, 1.5 Hz, 1H), 4.46 (tdd, *J* = 12.3, 5.3, 1.4 Hz, 1H), 4.07 (tdd, *J* = 12.5, 6.6, 1.2 Hz, 1H), 3.83 (td, , *J* = 11.0, 3.2 Hz, 1H), 3.63 (d, *J* = 2.9 Hz, 1H), 3.43-3.26 (m, 2H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.23-2.12 (m, 1H), 2.06-1.84 (m, 1H), 1.70-1.54 (m, 1H), 0.900 (d, *J* = 0.74 Hz, 3H), 0.877 (d, *J* = 0.73 Hz, 3H), 0.854 (s, 6H), 0.118 (s, 6H); ^{13}C NMR ($CDCl_3$); 135.7, 133.3, 127.4, 116.8, 77.3, 73.3, 71.8, 50.2, 34.1, 25.7, 24.9, 24.8, 20.9, 20.3, 18.6, 18.5, -2.59, -2.63; HR MS (CI, CH_4): calcd for $C_{19}H_{35}O_2N_3Si$+ H: m/z 366.2577; found: 366.2549.

APPENDIX
SPECTRAL DATA

The ^{1}H and ^{13}C or APT NMR spectra of selected compounds reported in Chapter 5 are shown in this appendix along with the proposed structures.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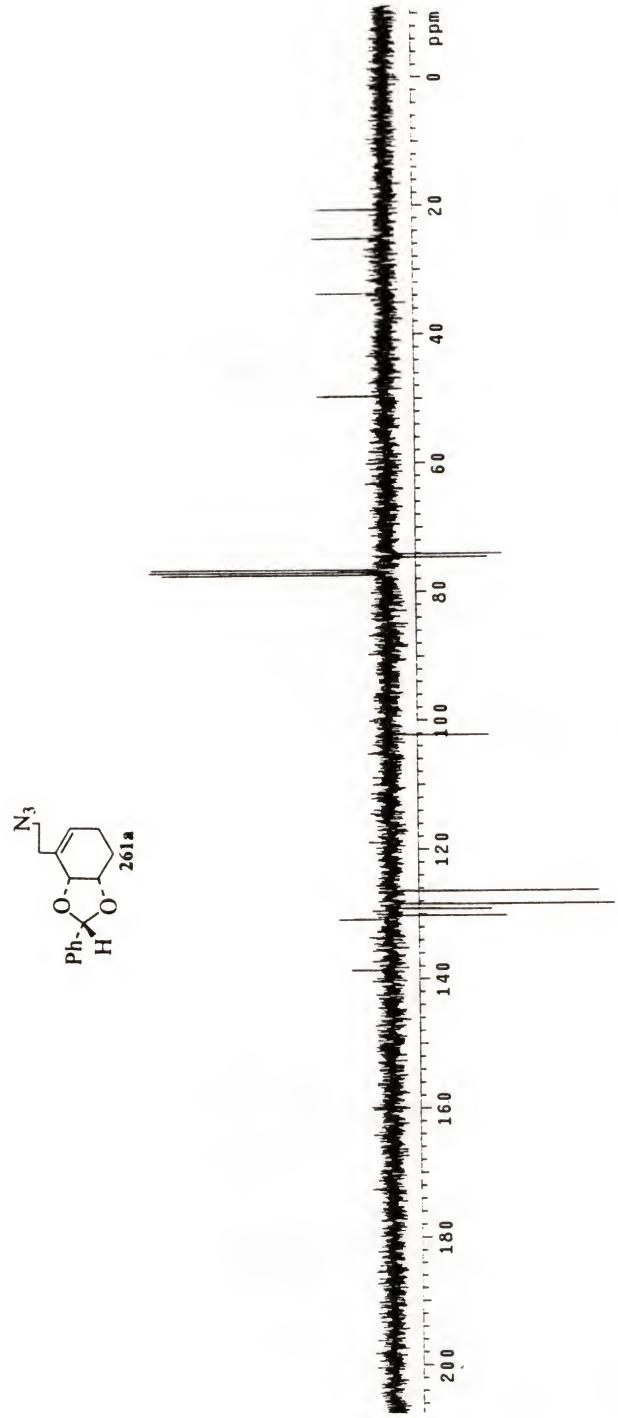
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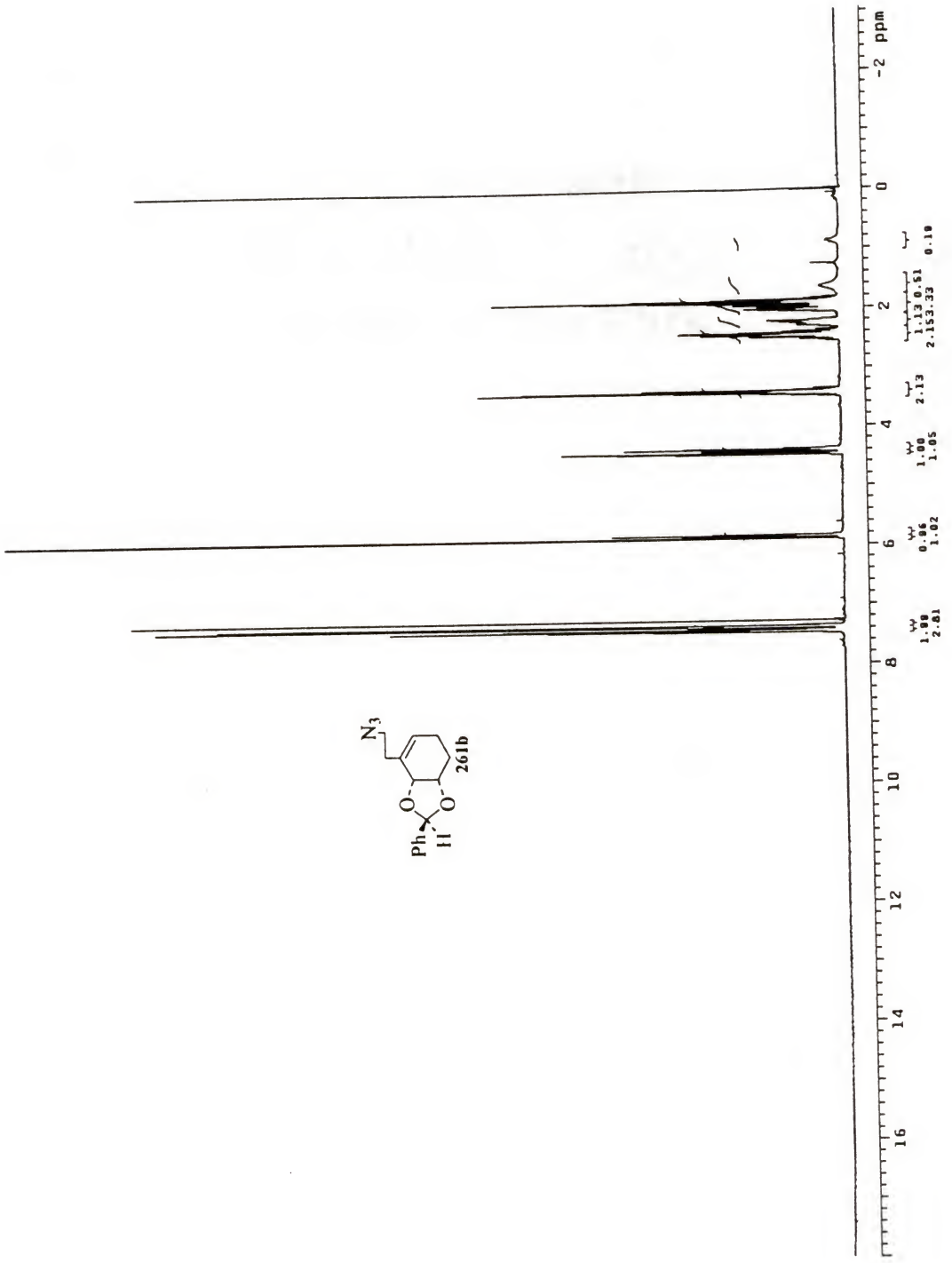
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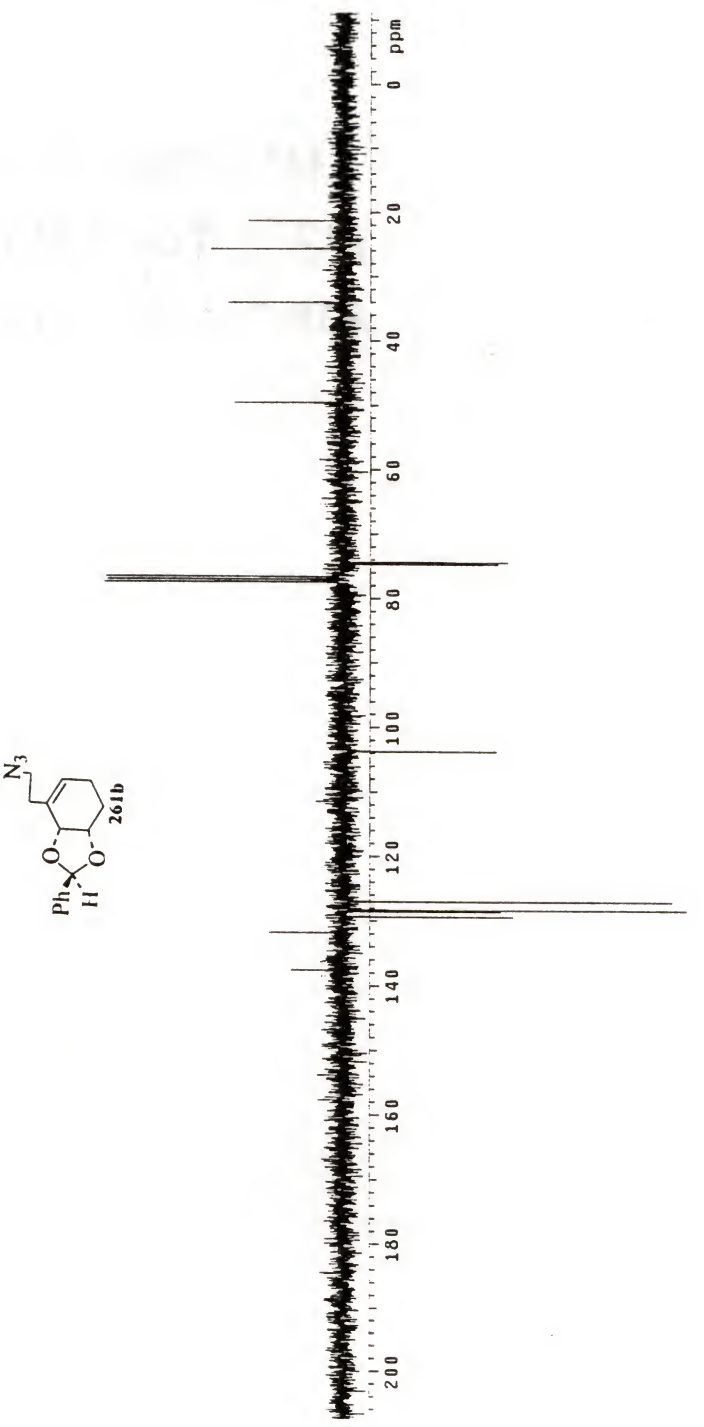
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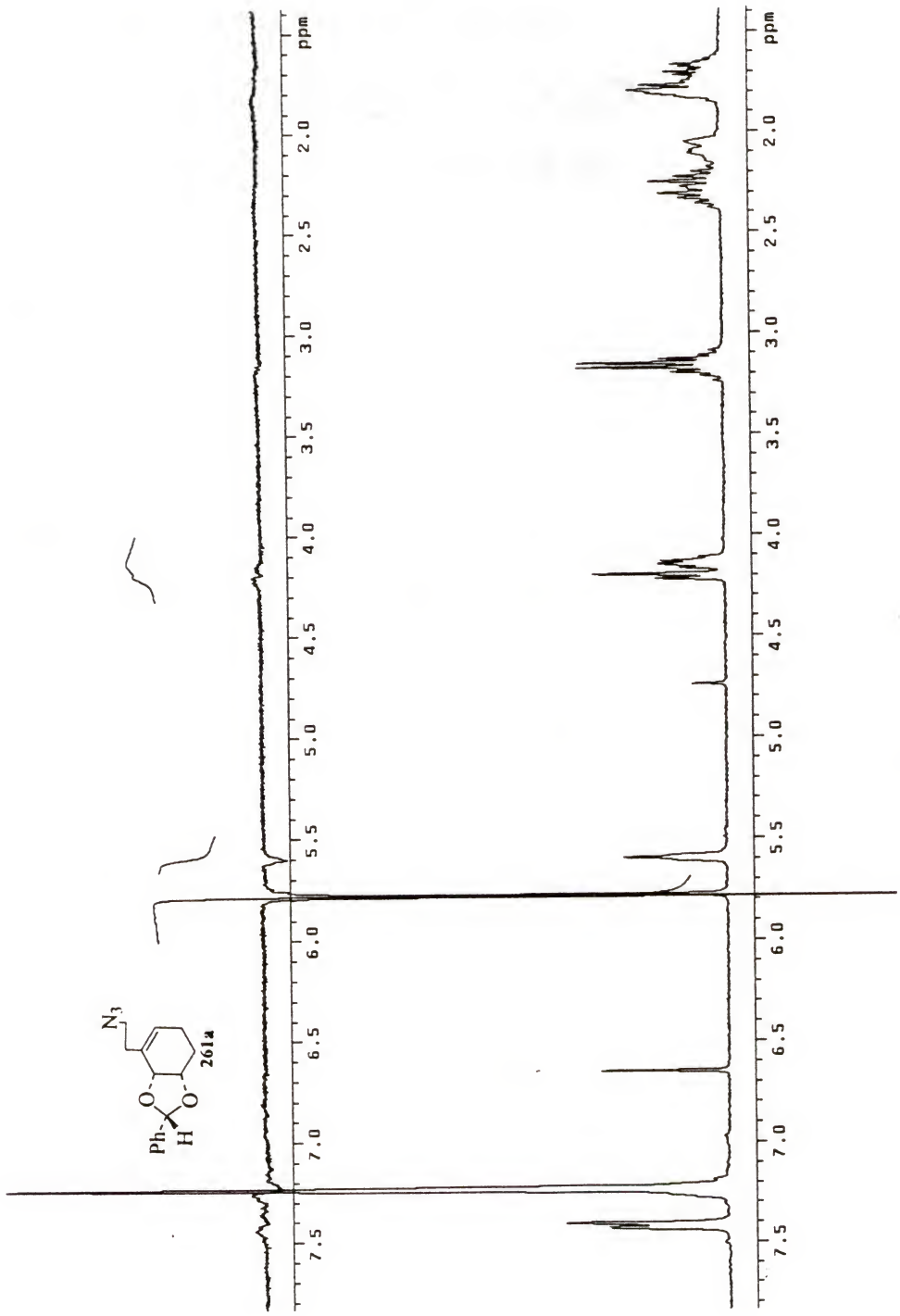
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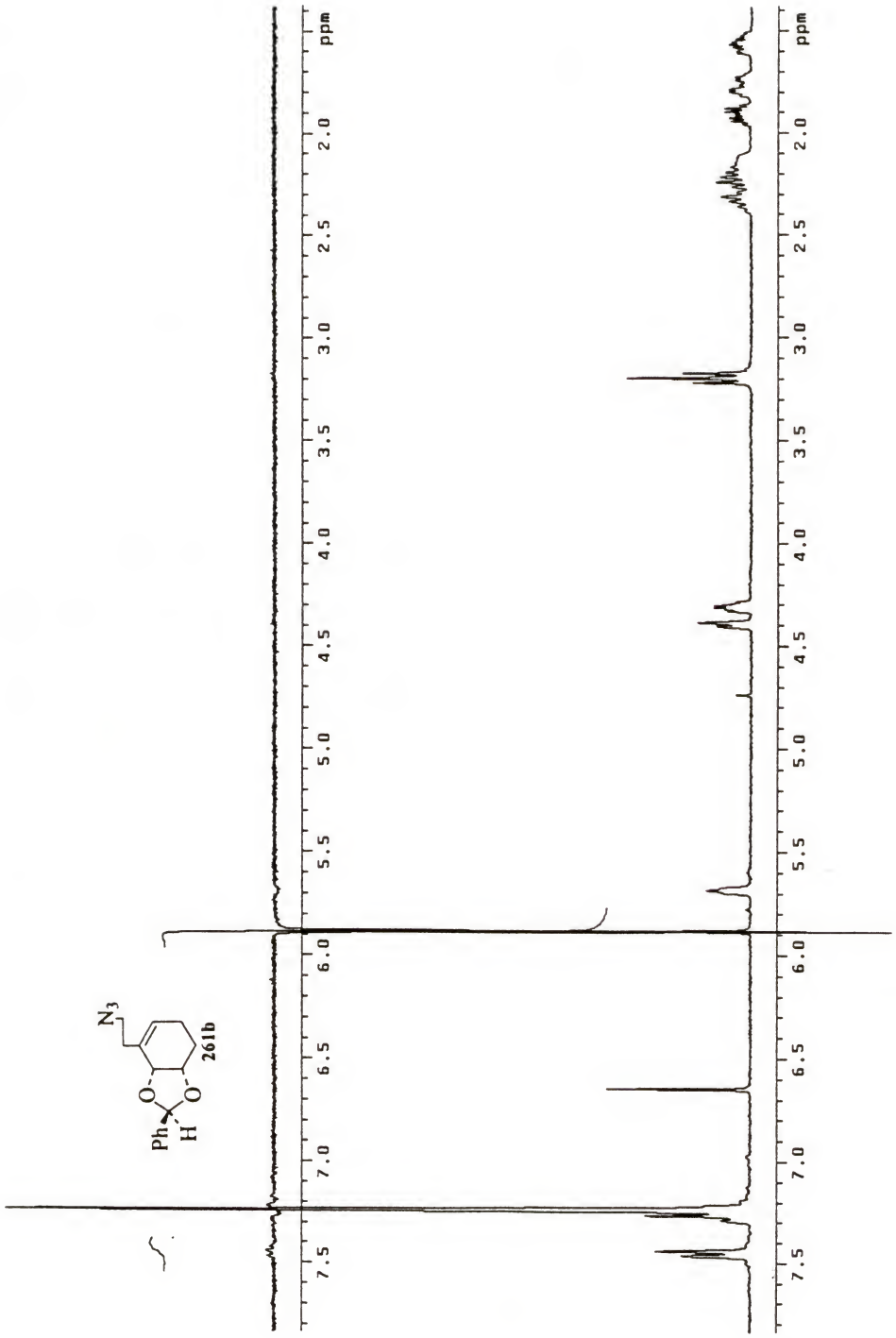
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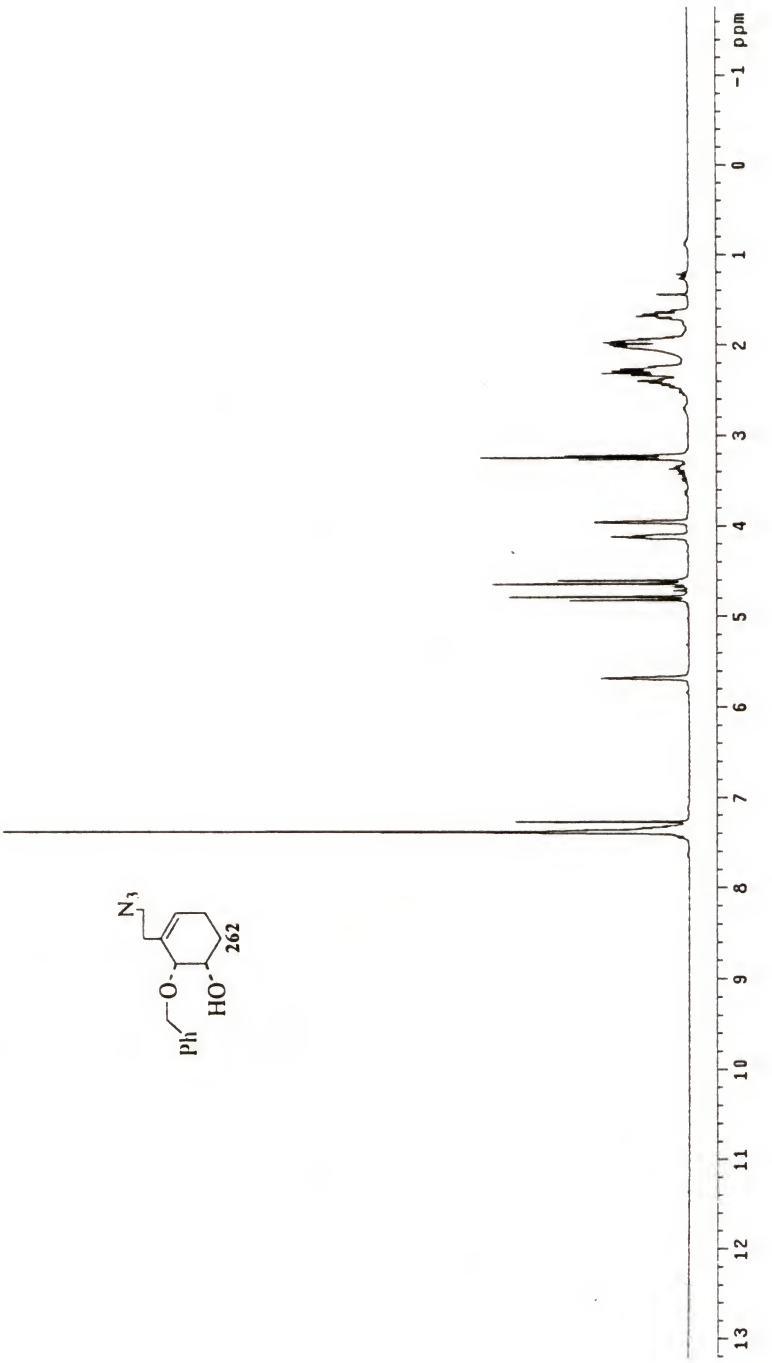
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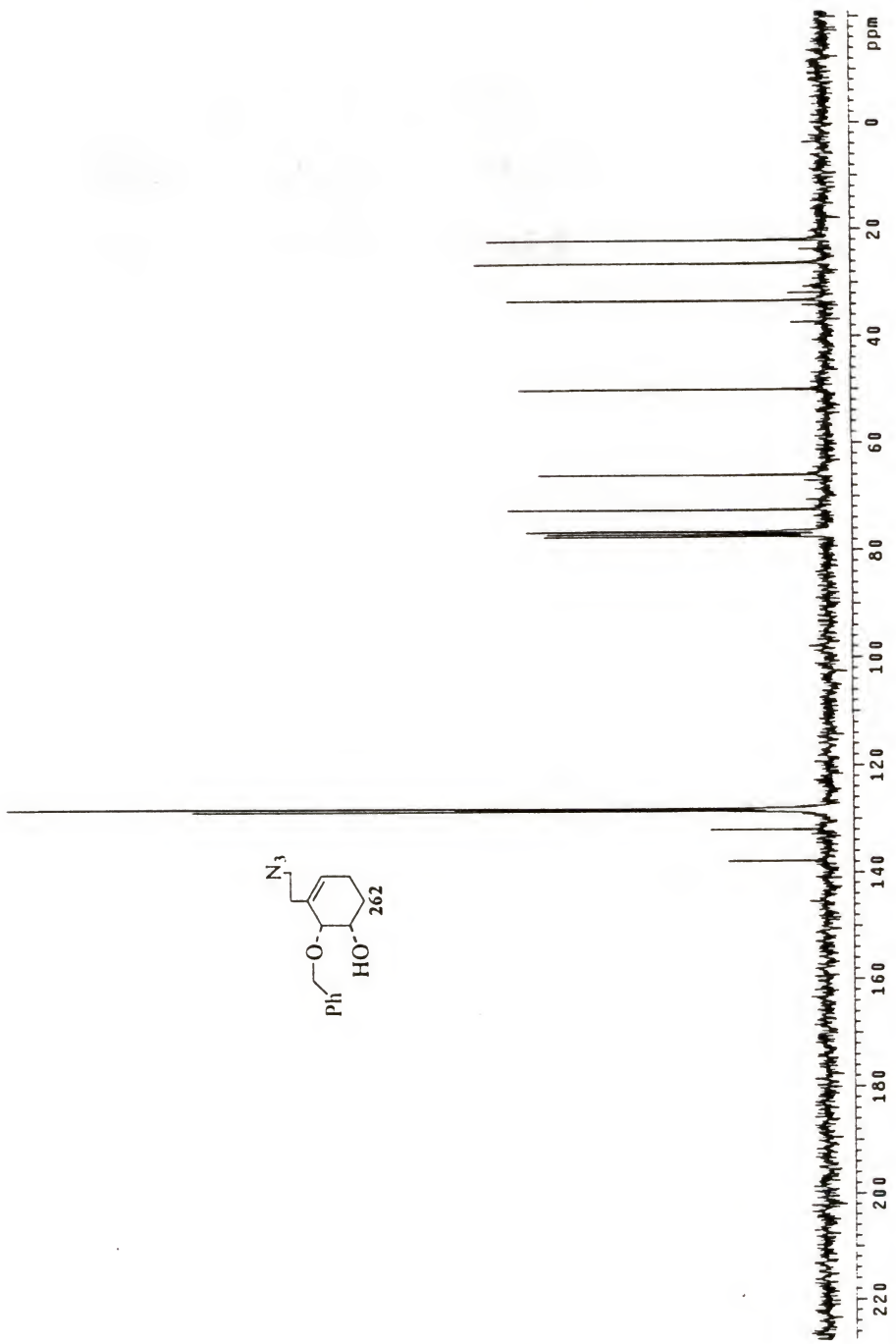
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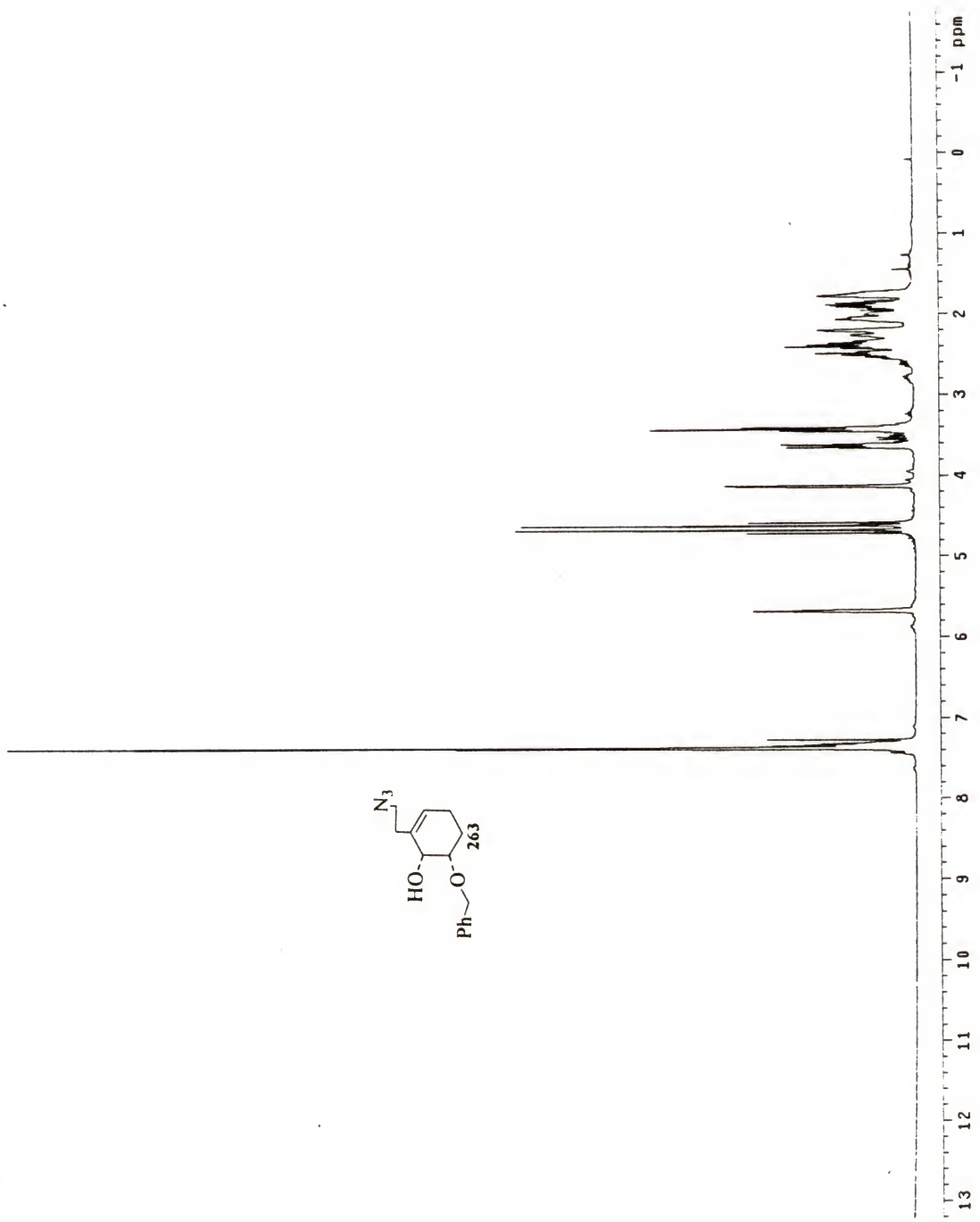
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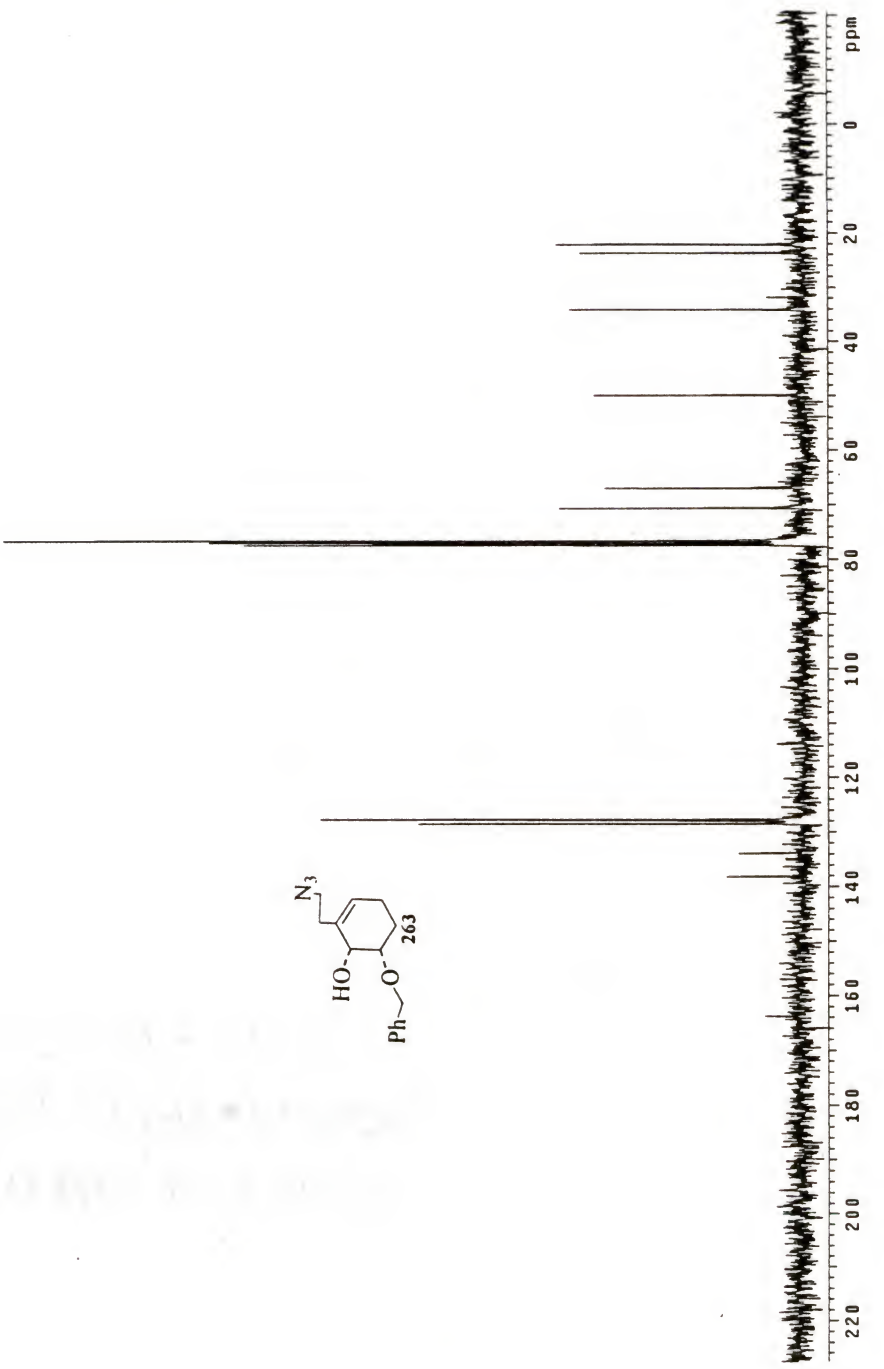
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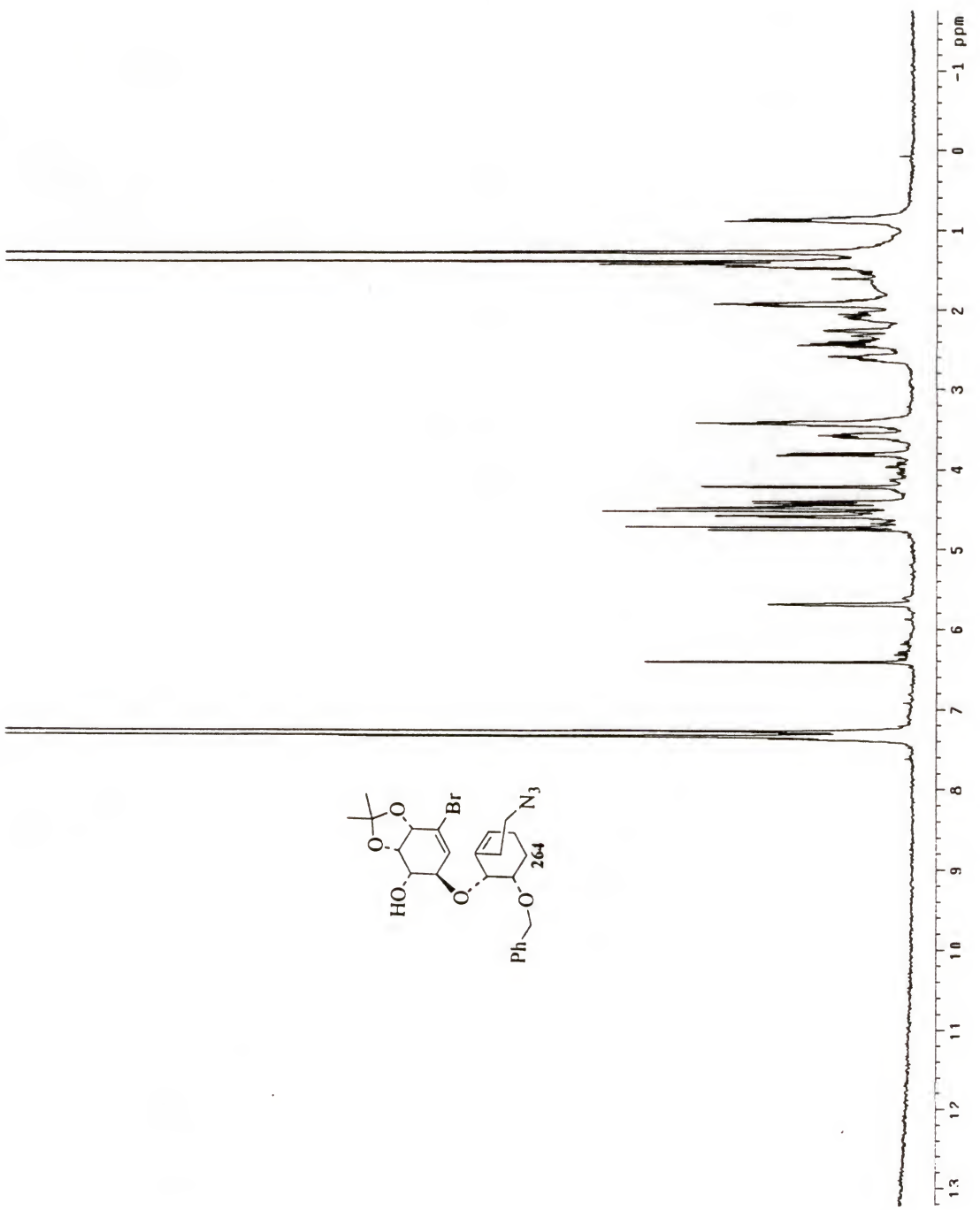
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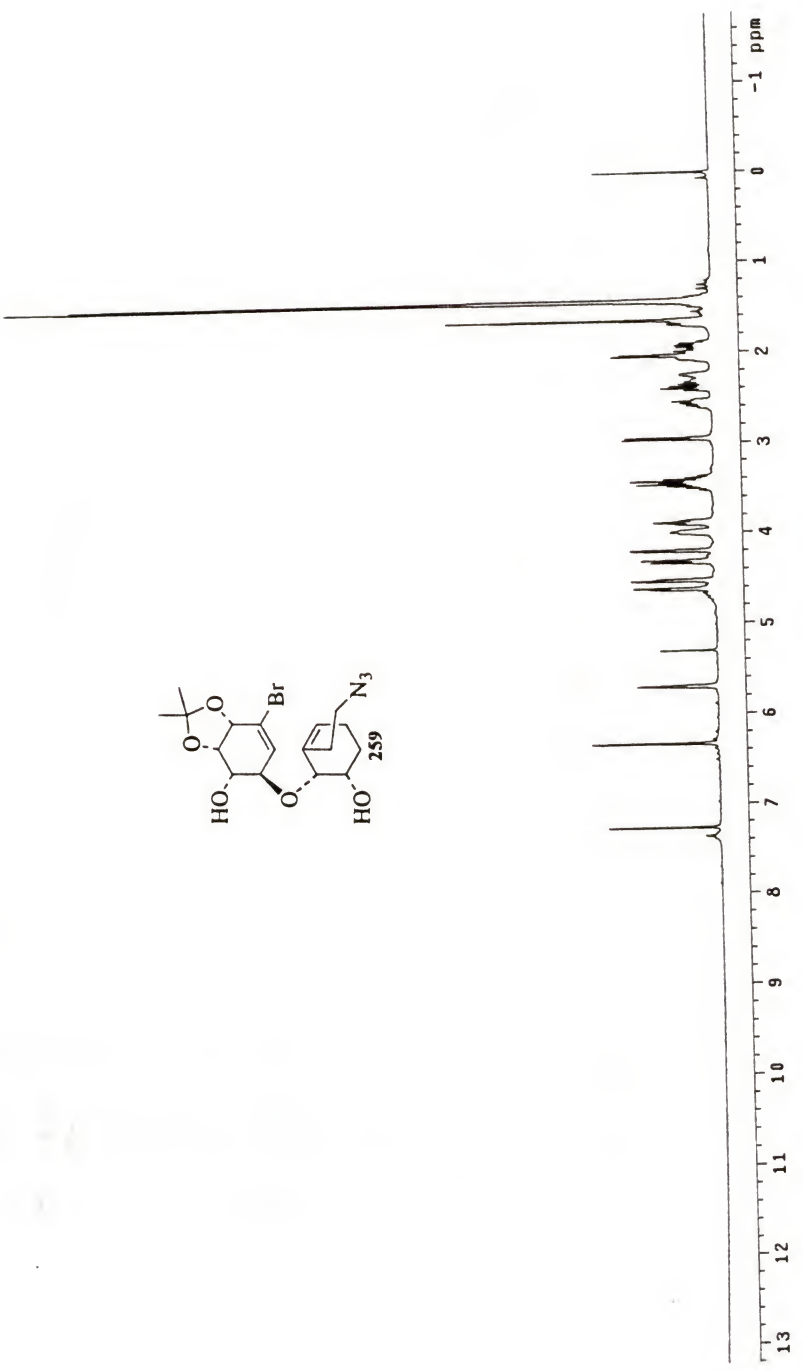
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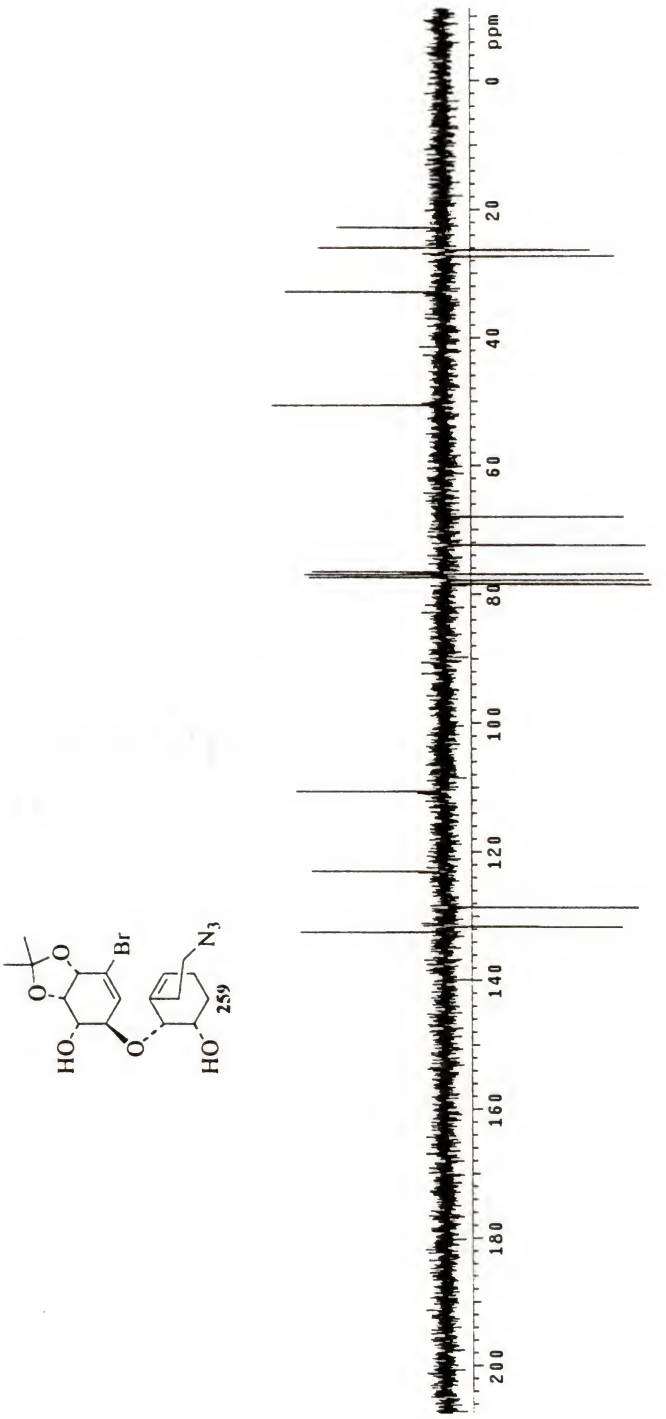
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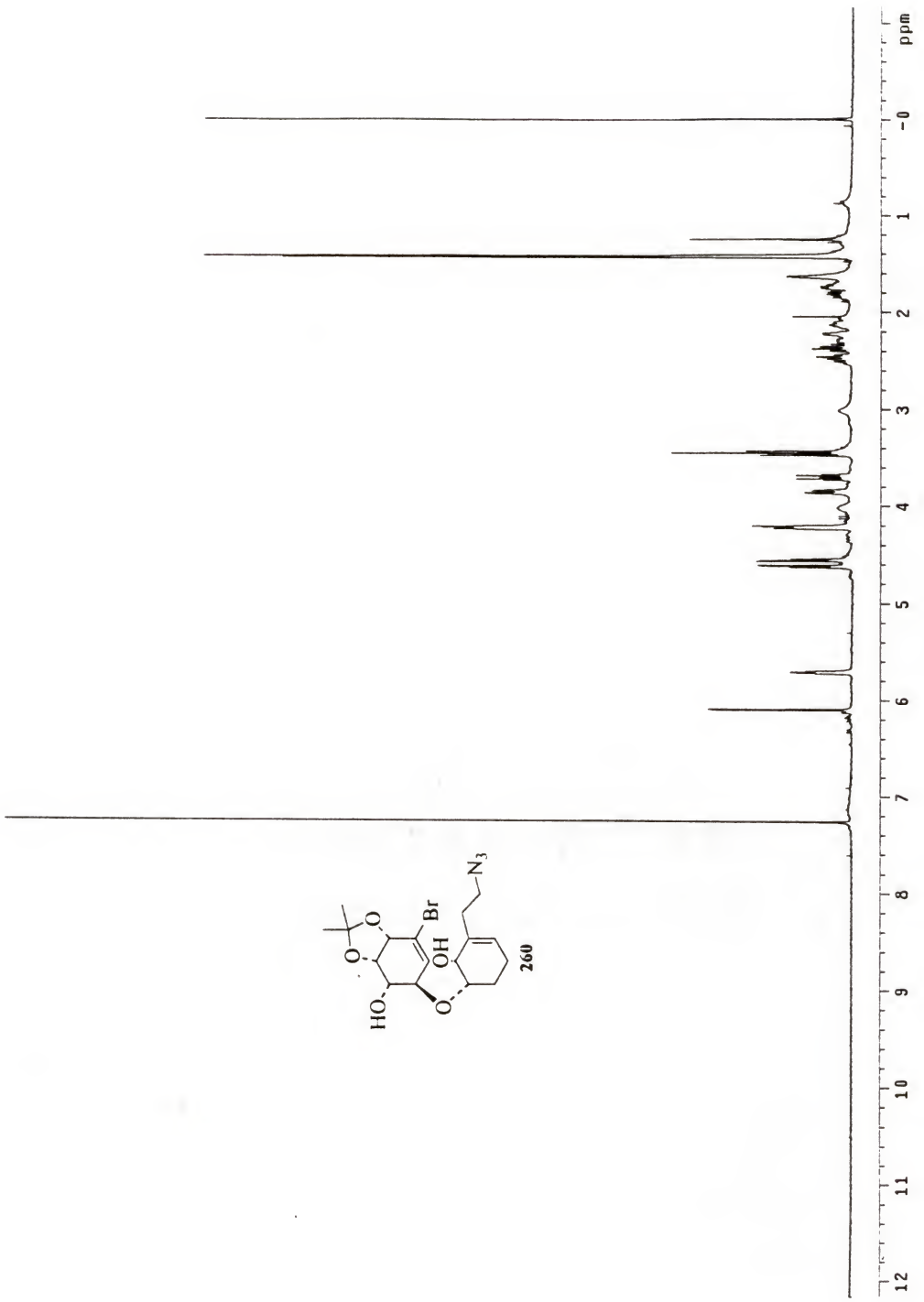
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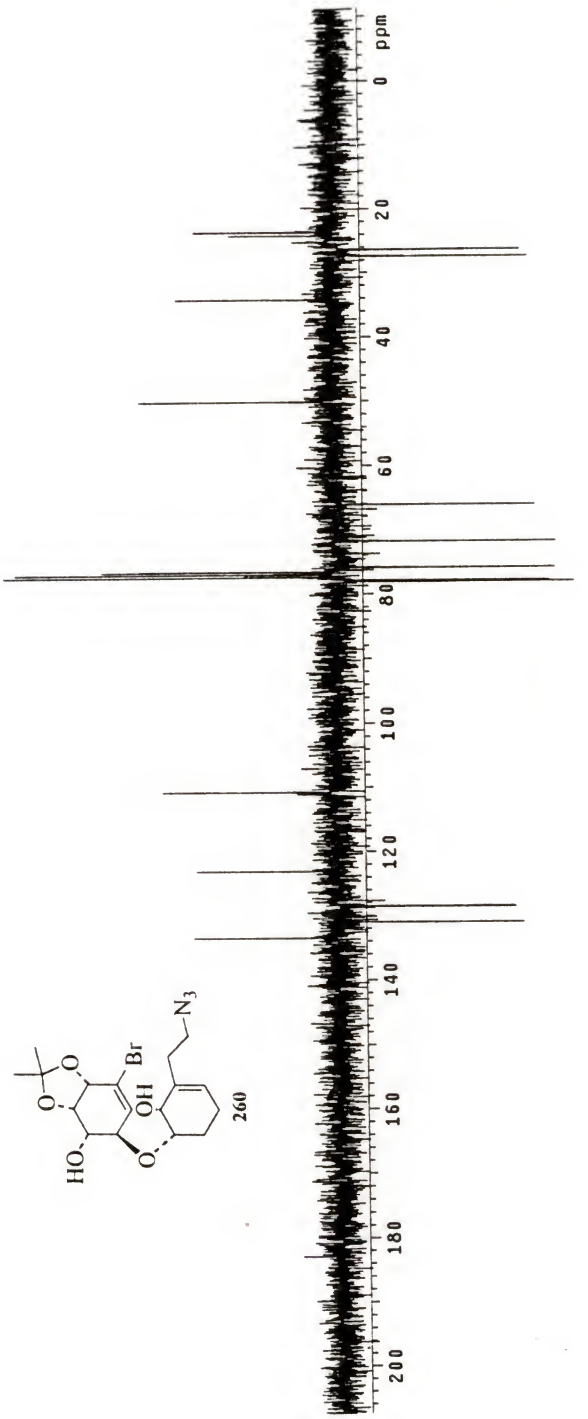
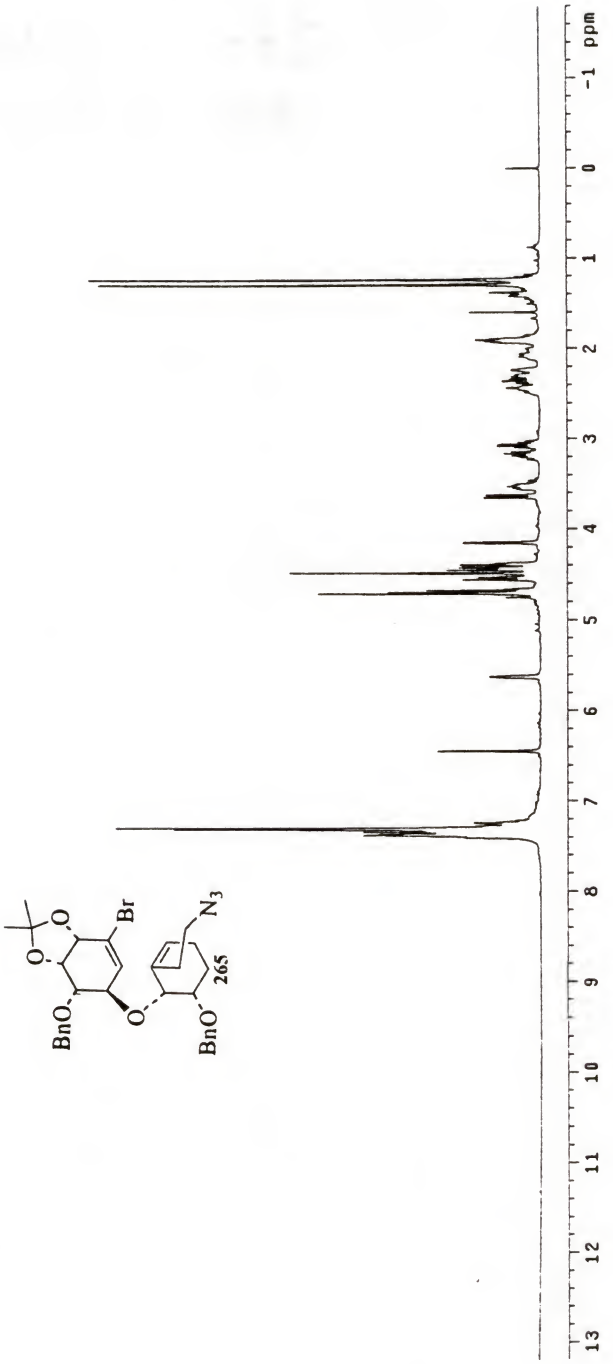
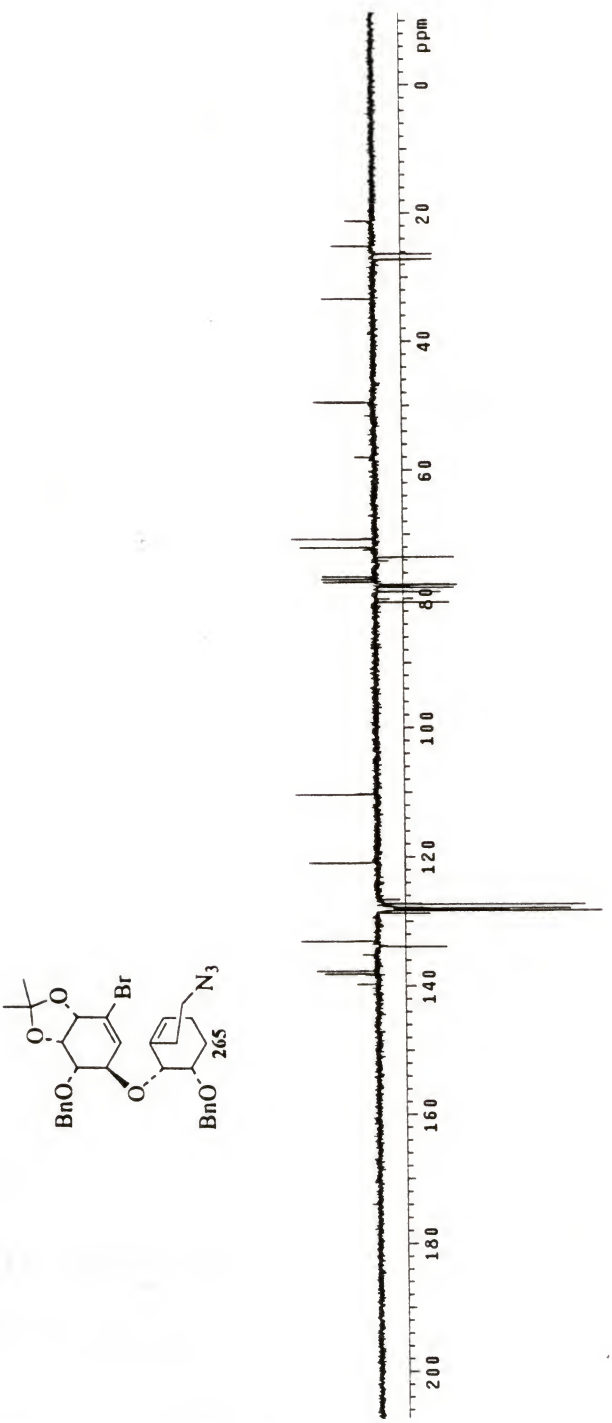
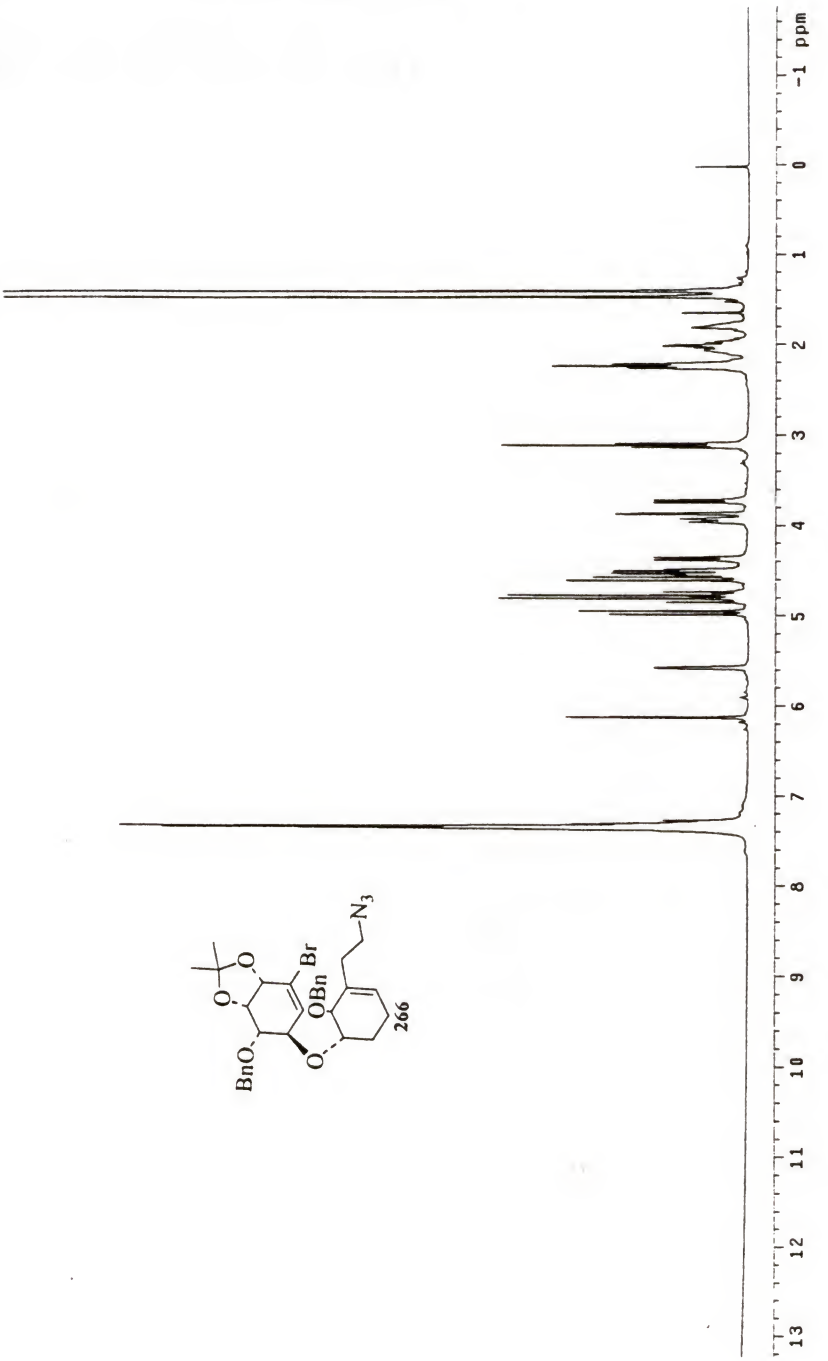
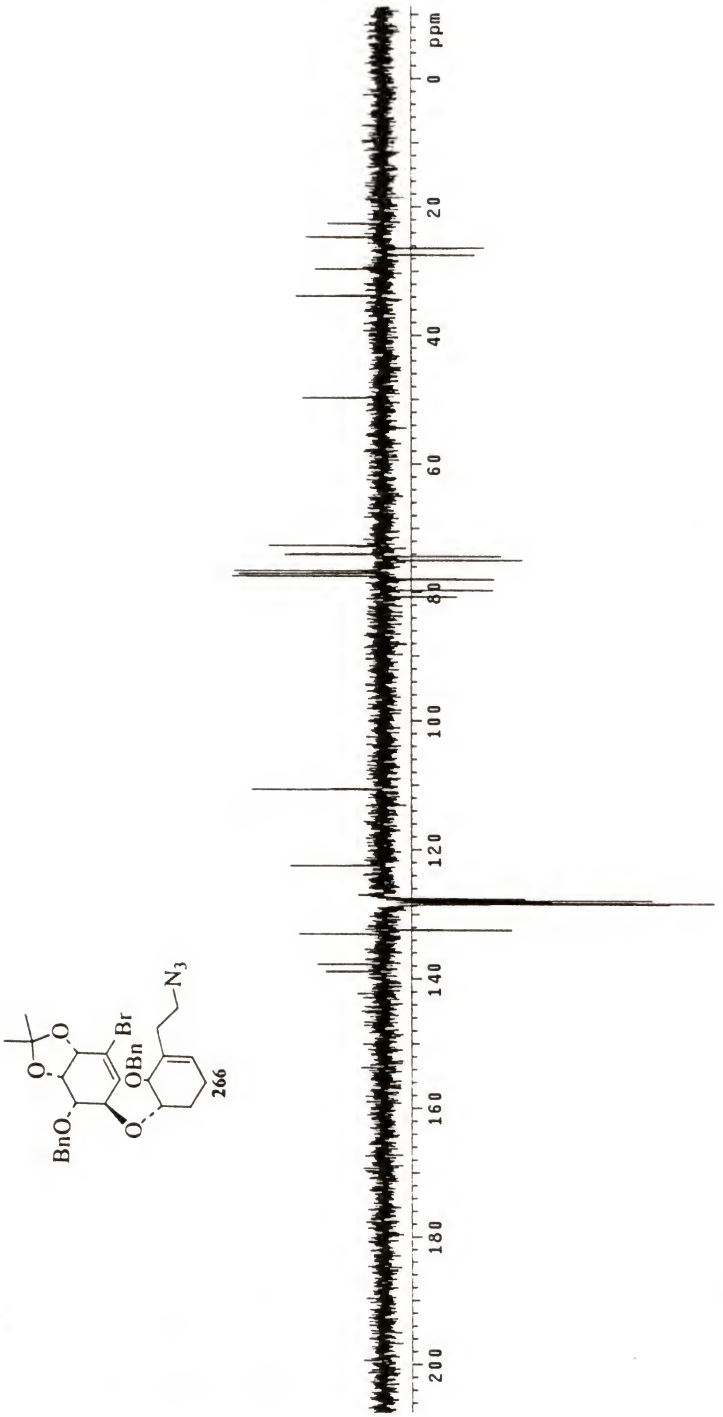
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0

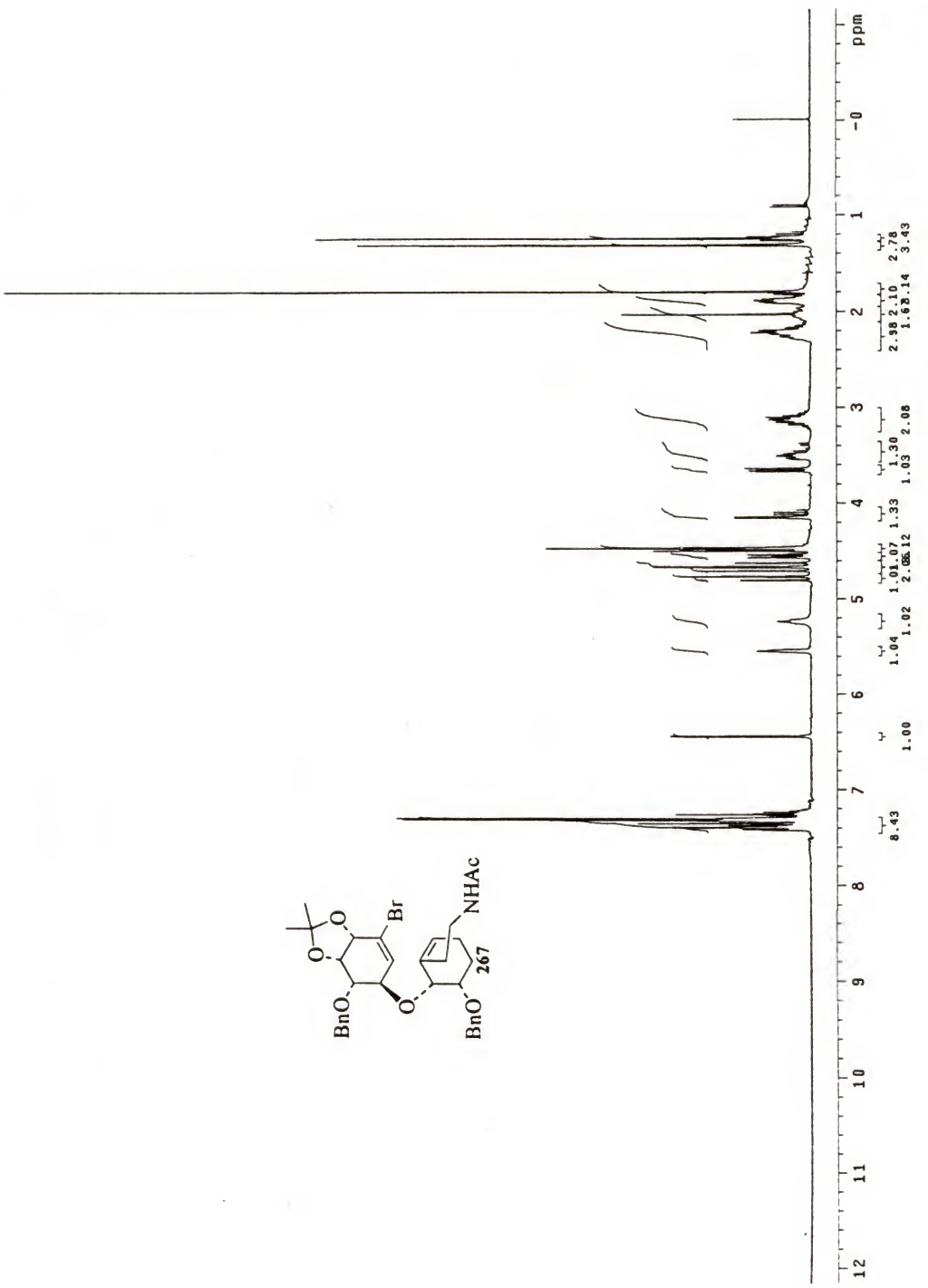

0 ppm
20
40
60
80
100
120
140
160
180
200
Br
OH
HO
O
O
O
N_3
260

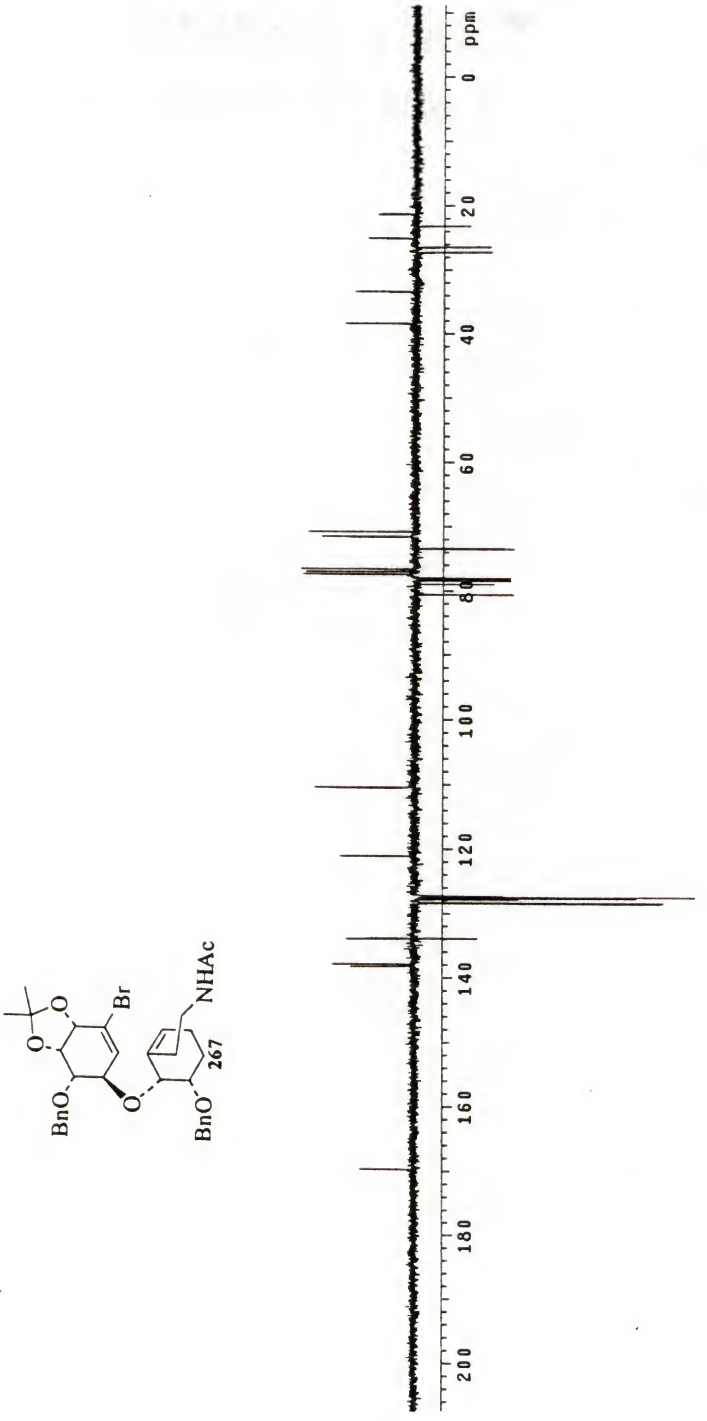

Br
BnO
O
BnO
265
N3
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm

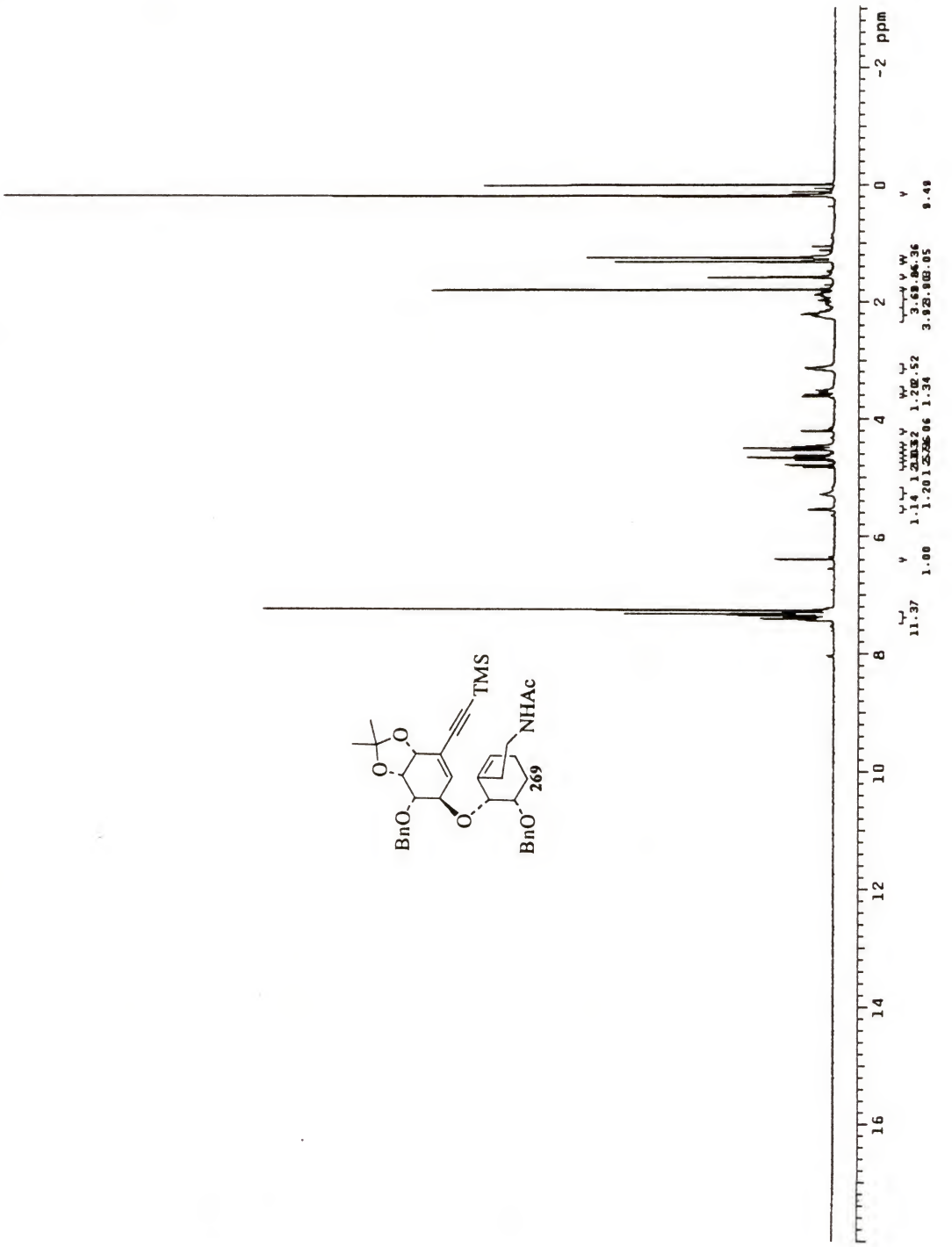

Br
N3
BnO
O
BnO
265
ppm
0
20
40
60
80
100
120
140
160
180
200

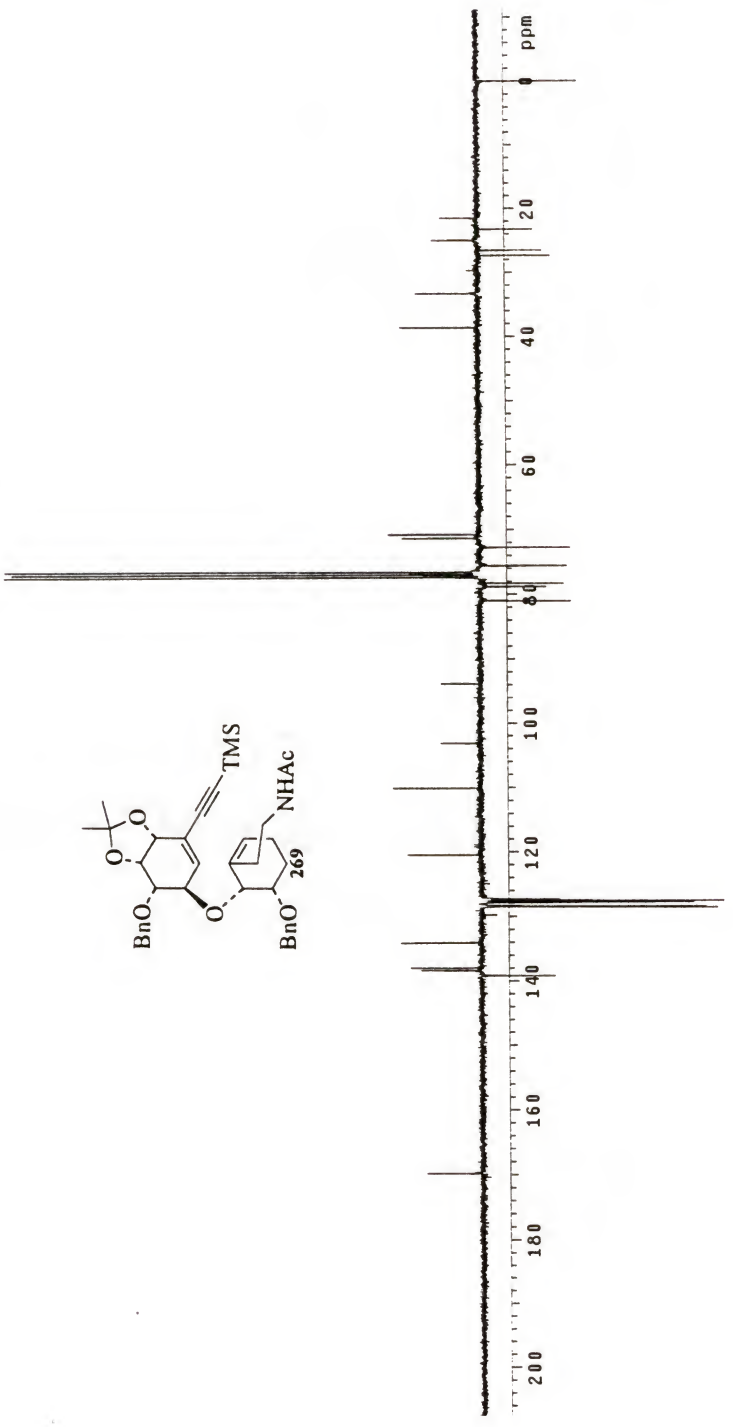

BnO
O
O
Br
OBn
O
N_3
266
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm

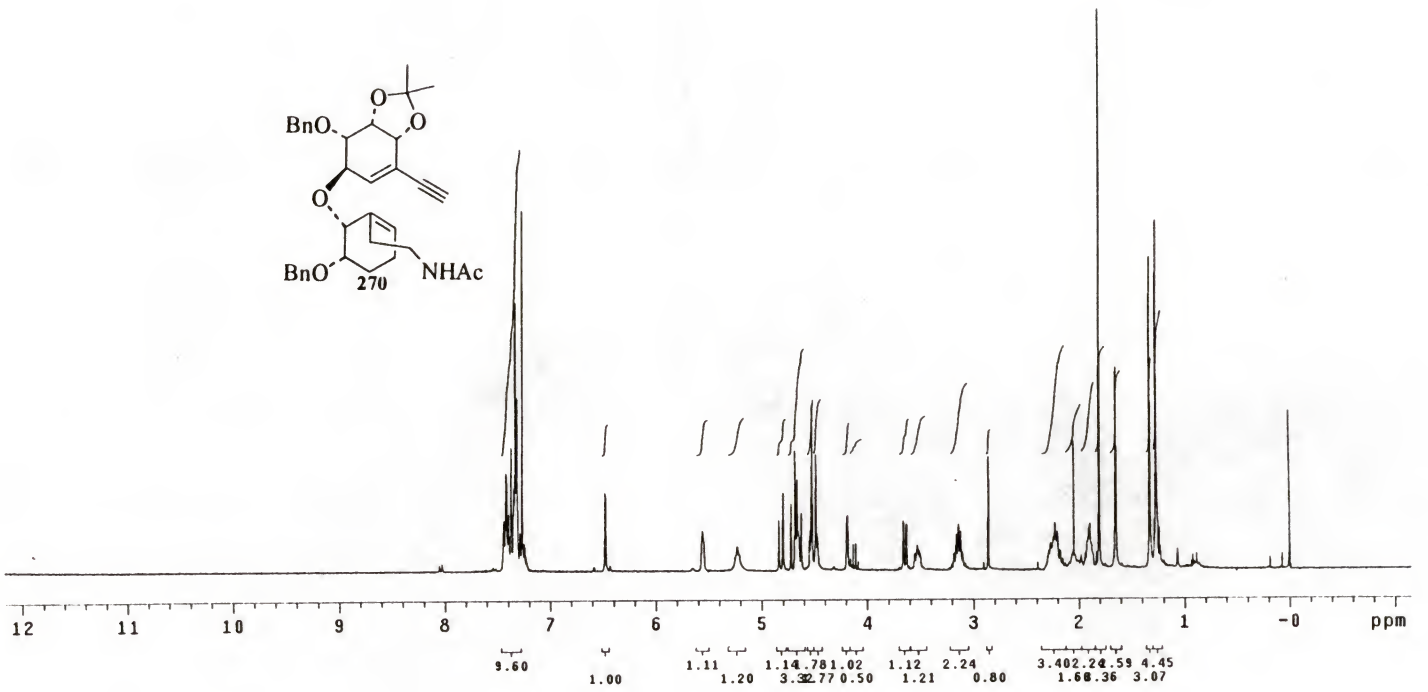

BnO
OBn
Br
N_3
266
200
180
160
140
120
100
80
60
40
20
0 ppm

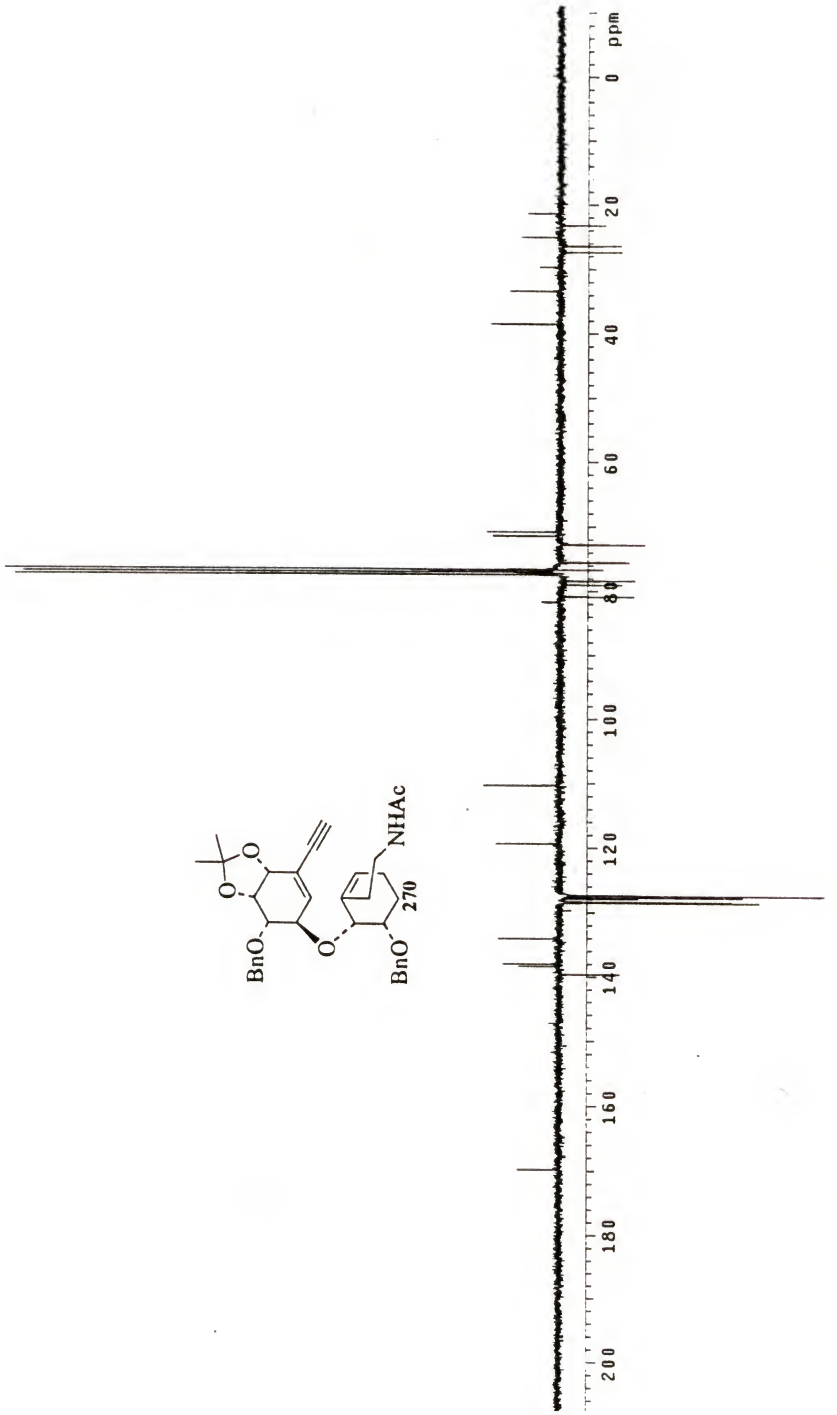

BnO
Br
O
BnO
NHAc
267
ppm

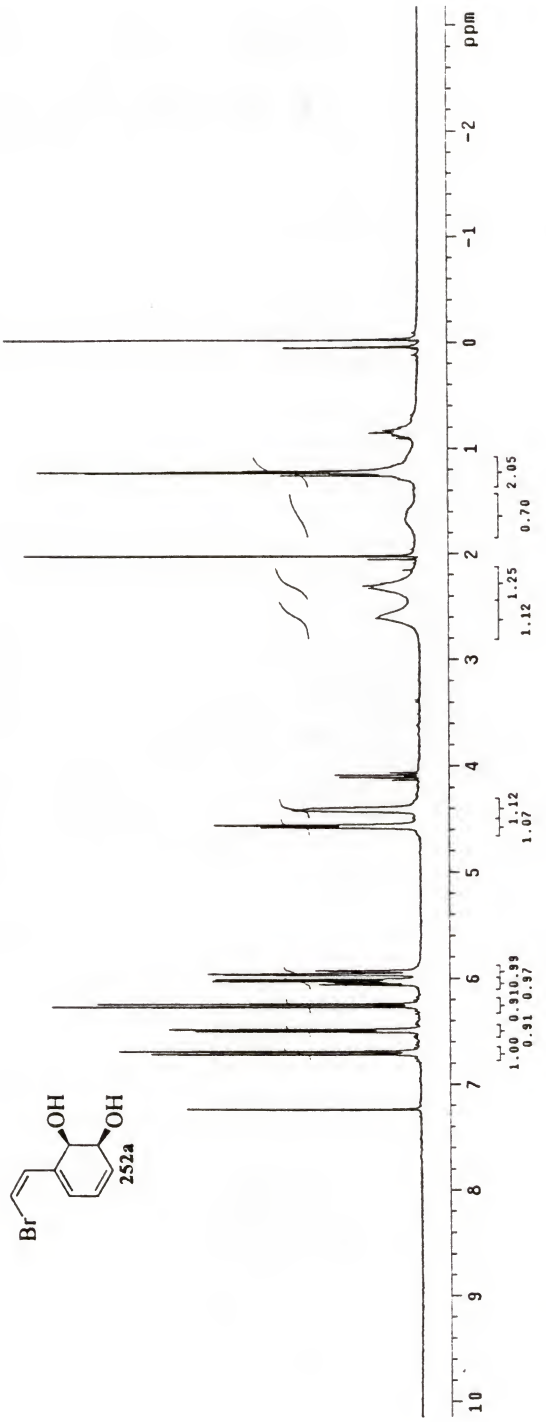

BnO
O
O
Br
O
BnO
NHAc
267
ppm
0
20
40
60
80
100
120
140
160
180
200

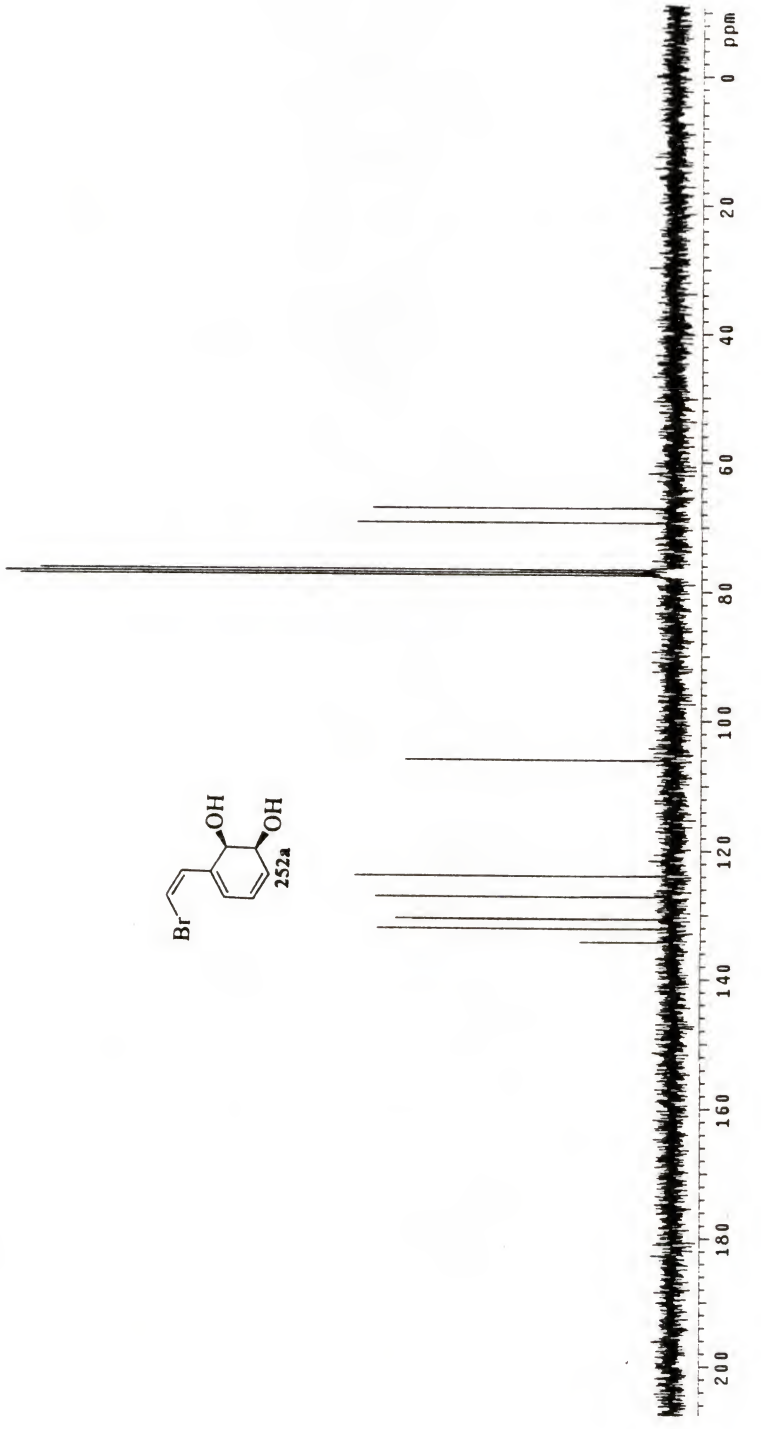

TMS
NHAc
BnO
BnO
269
-2 ppm

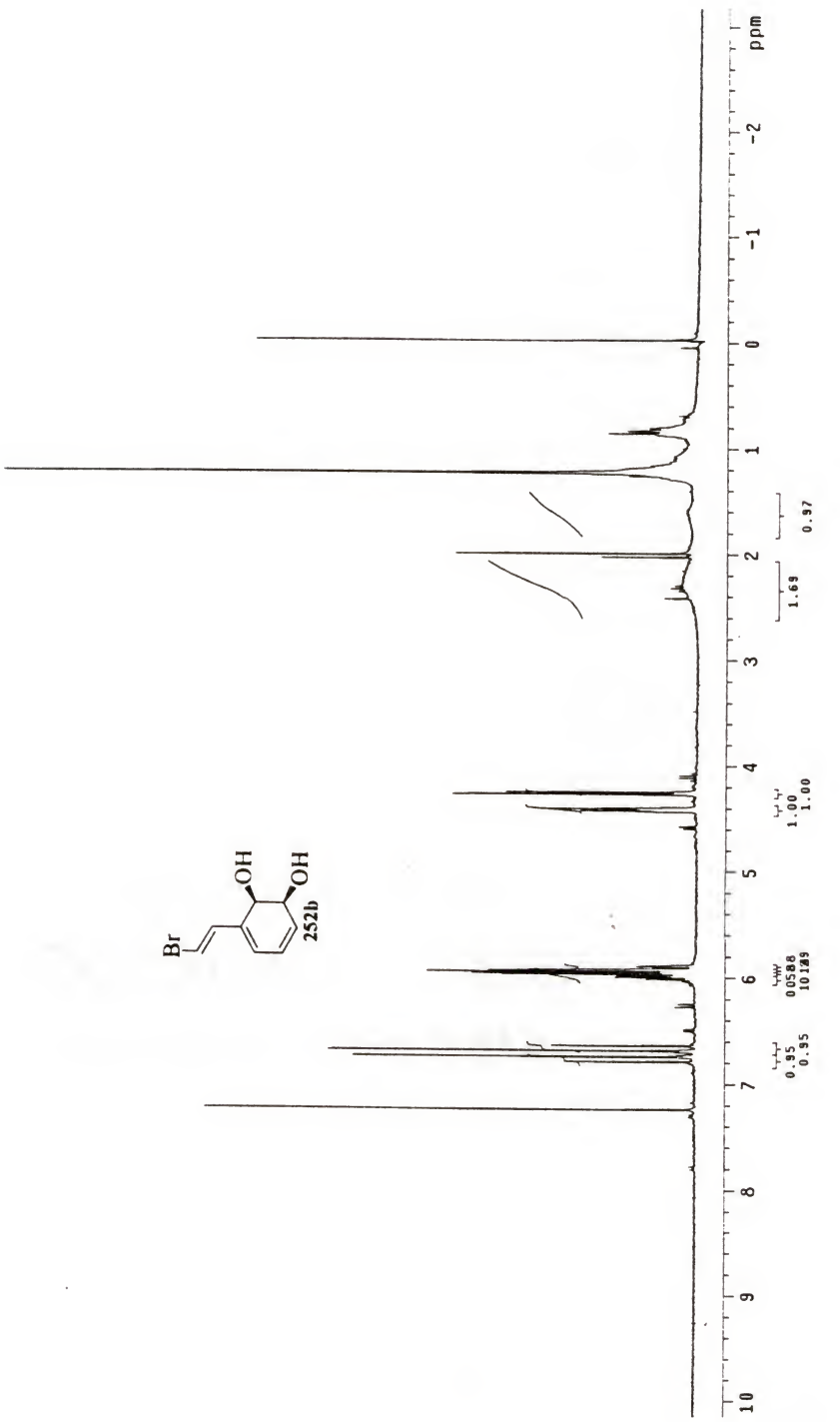

TMS
NHAc
BnO
BnO
269
ppm
0
20
40
60
80
100
120
140
160
180
200

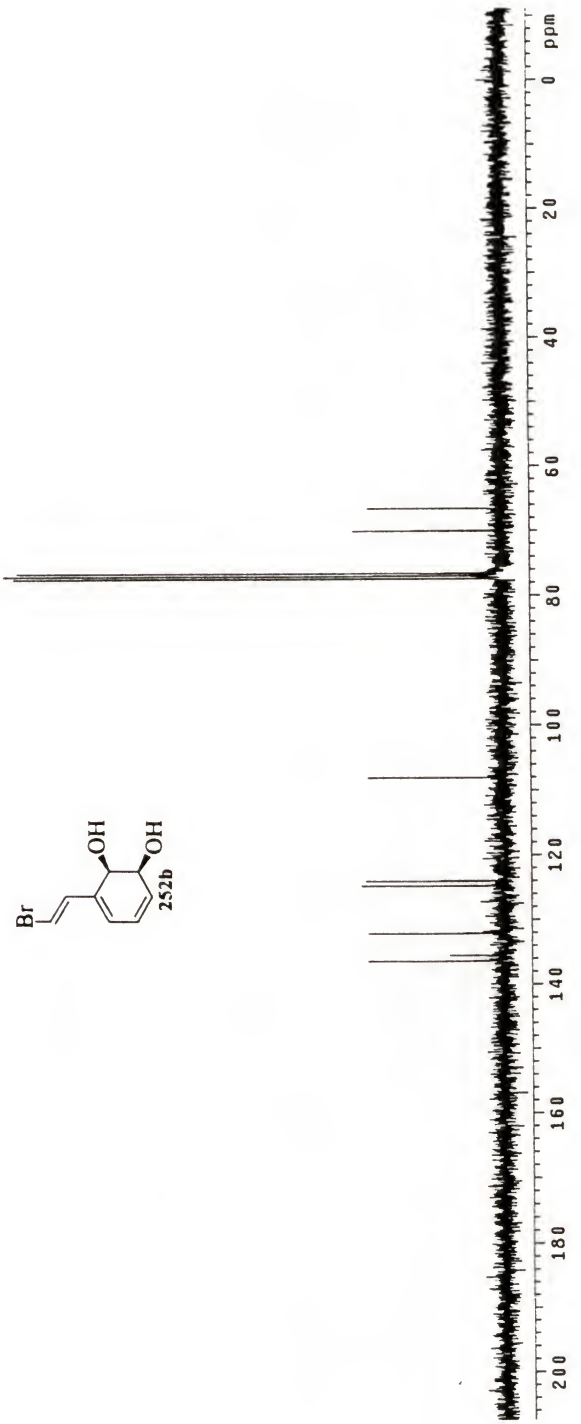

BnO
O
O
O
BnO
NHAc
270
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
9.60
1.00
1.11
1.20
1.14
3.32
4.78
2.77
1.02
0.50
1.12
1.21
2.24
0.80
3.40
1.66
2.26
8.36
4.59
3.07
4.45

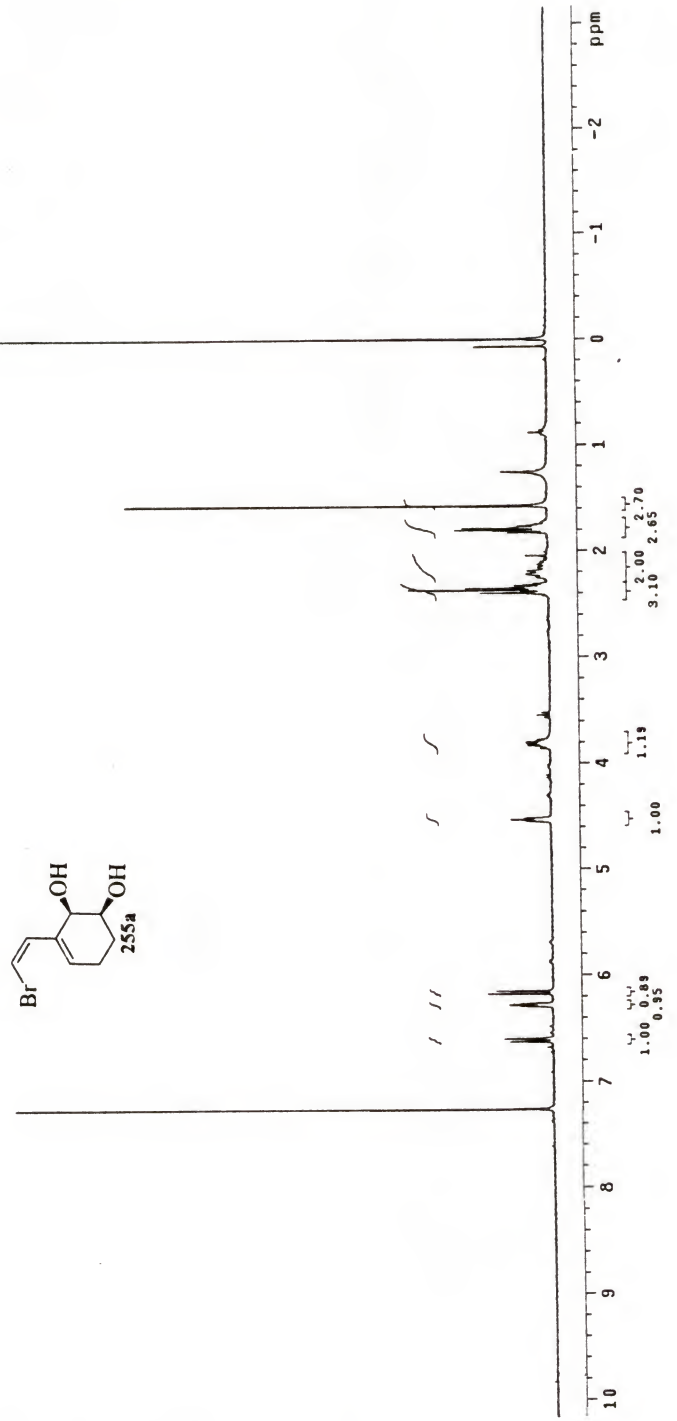

NHAc
BnO
BnO
270
0 ppm
20
40
60
80
100
120
140
160
180
200

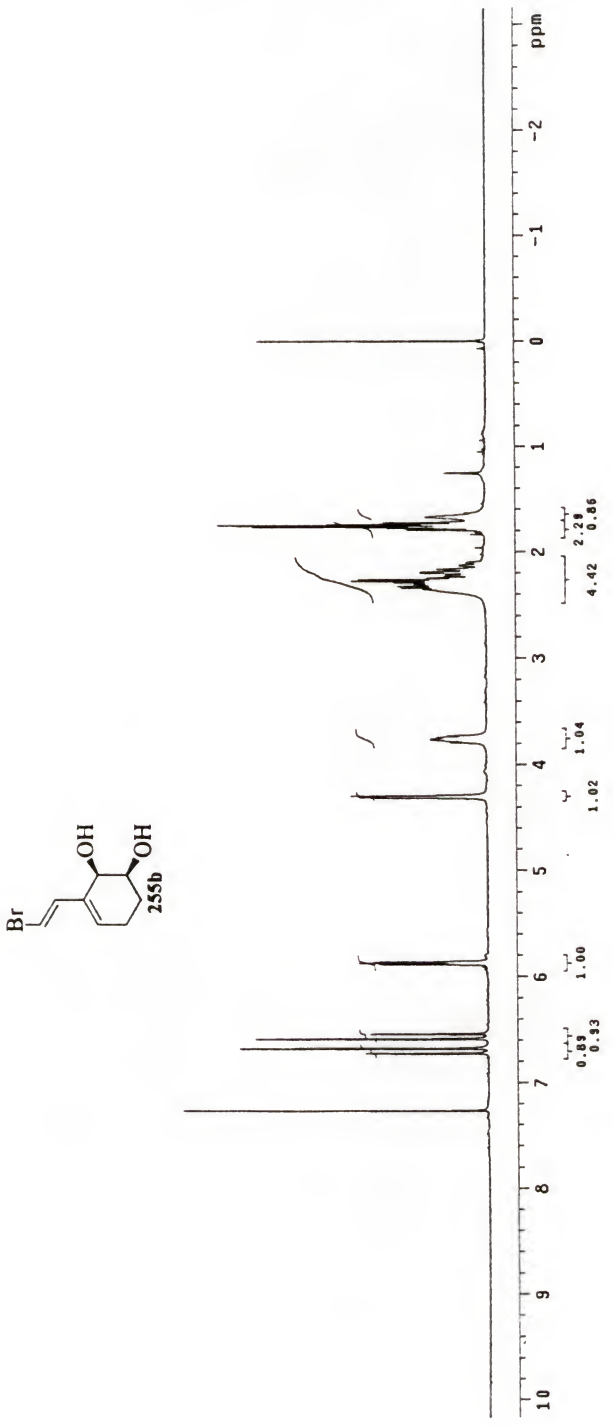

OH
OH
Br
252a
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
1.00 0.91 0.91 0.99 0.97
1.12 1.07
1.12 1.25 2.05 0.70

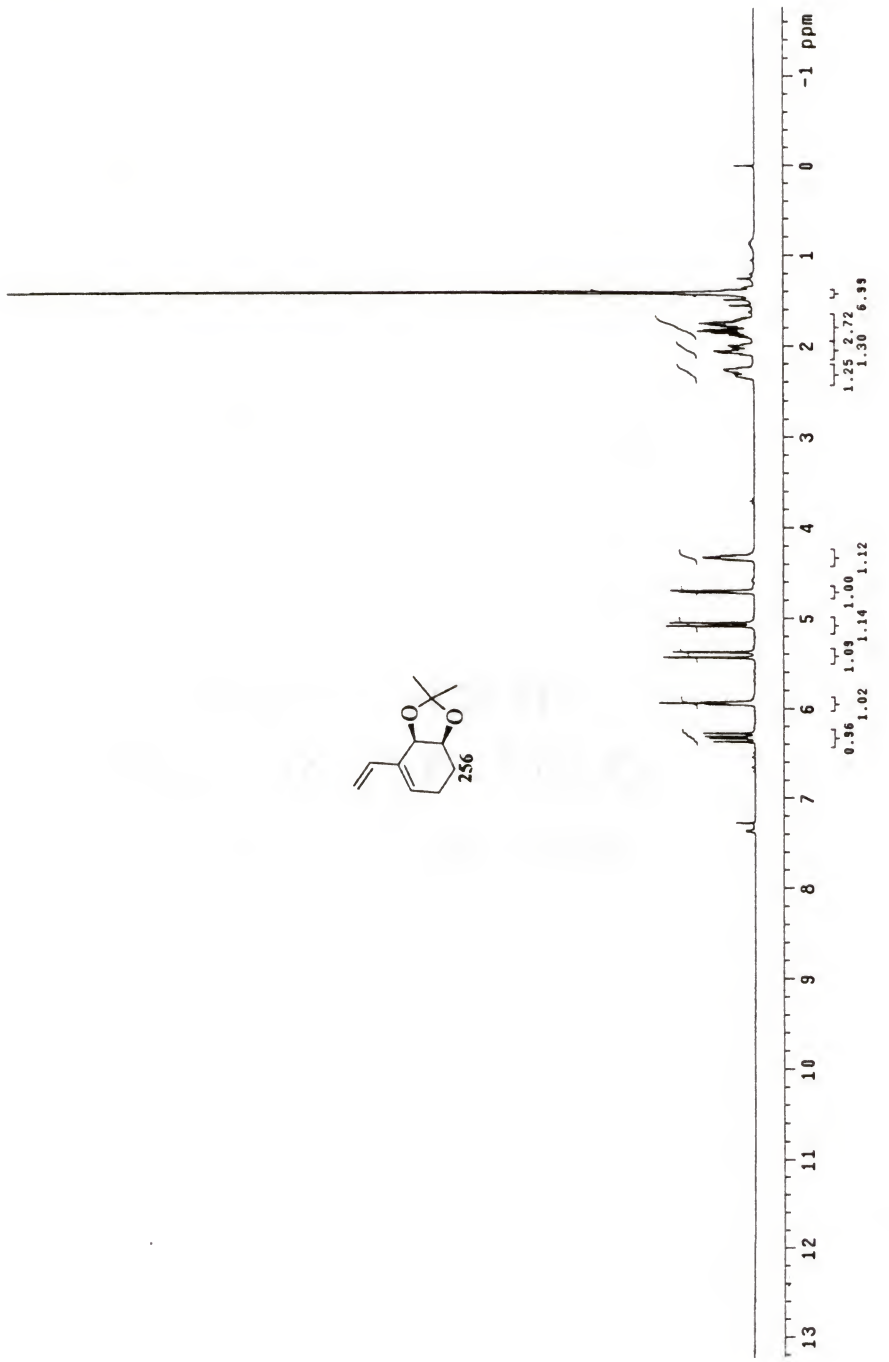

OH
OH
Br
252a
200
180
160
140
120
100
80
60
40
20
0
ppm

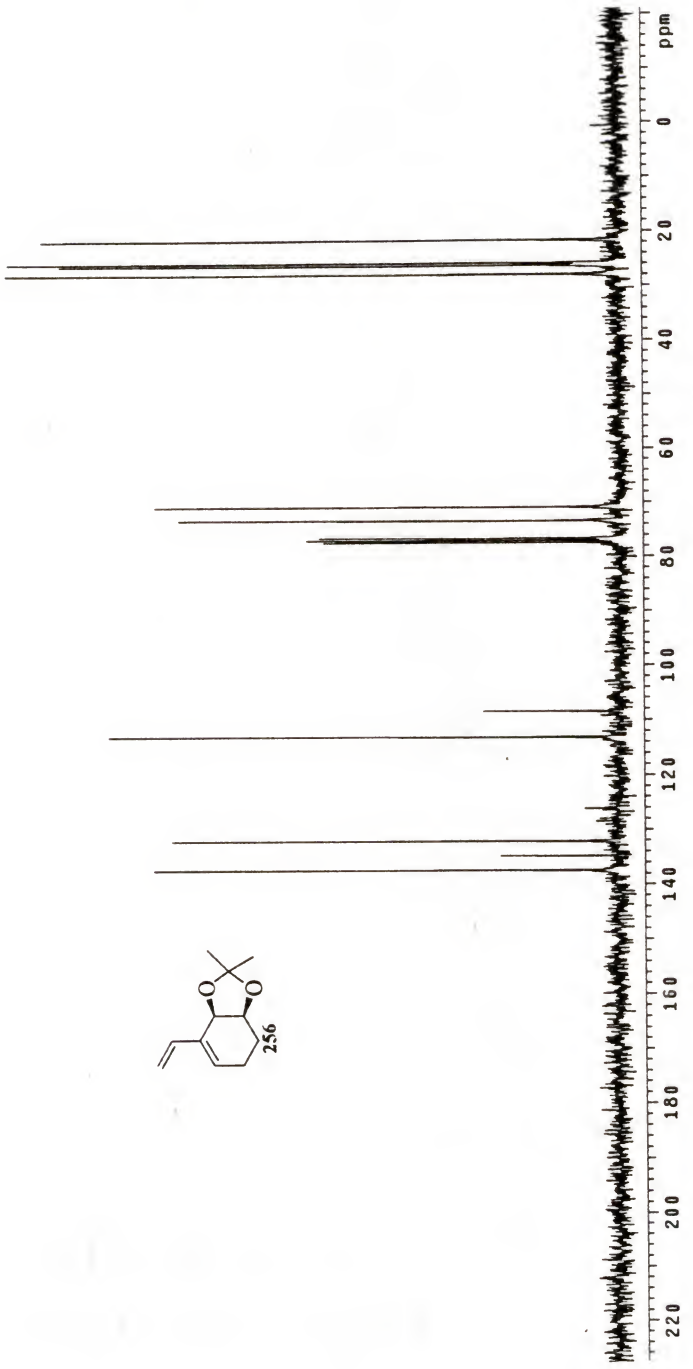

Br
OH
OH
252b
ppm

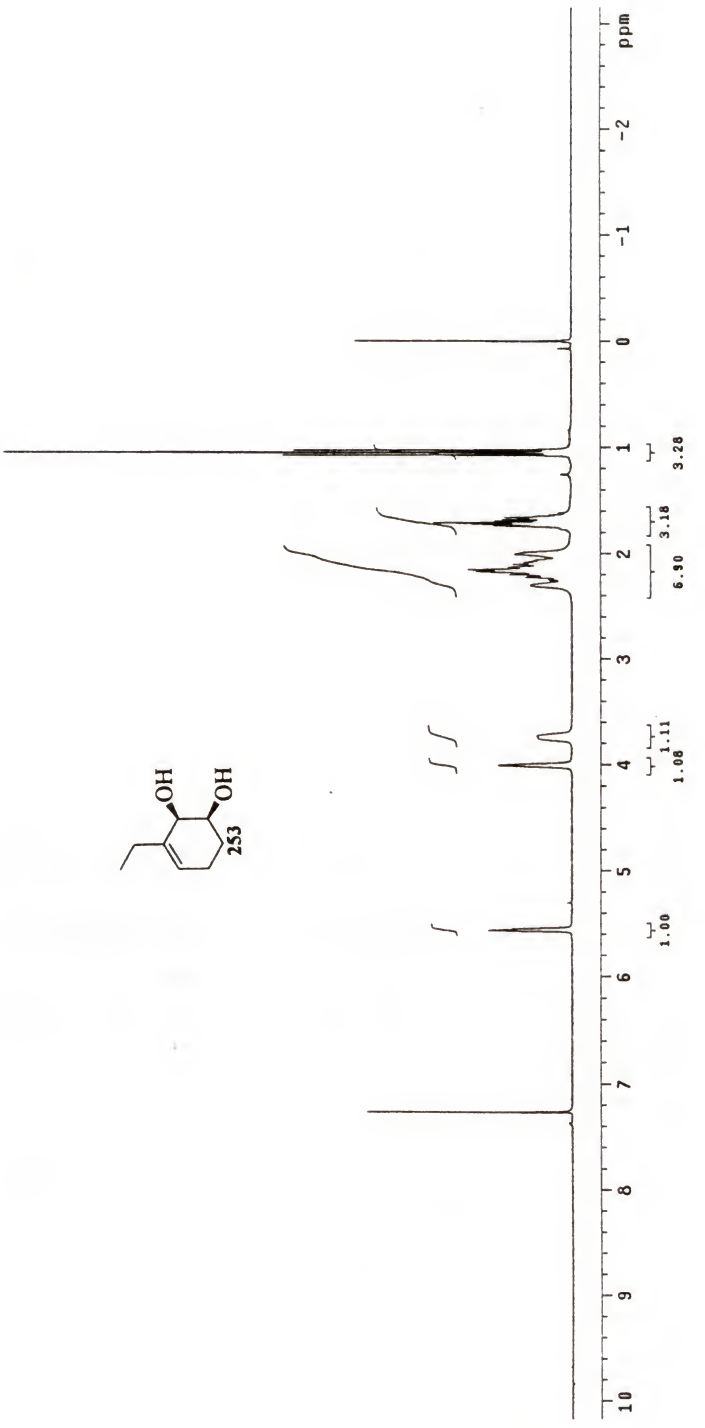

OH
OH
Br
252b
200
180
160
140
120
100
80
60
40
20
0
ppm

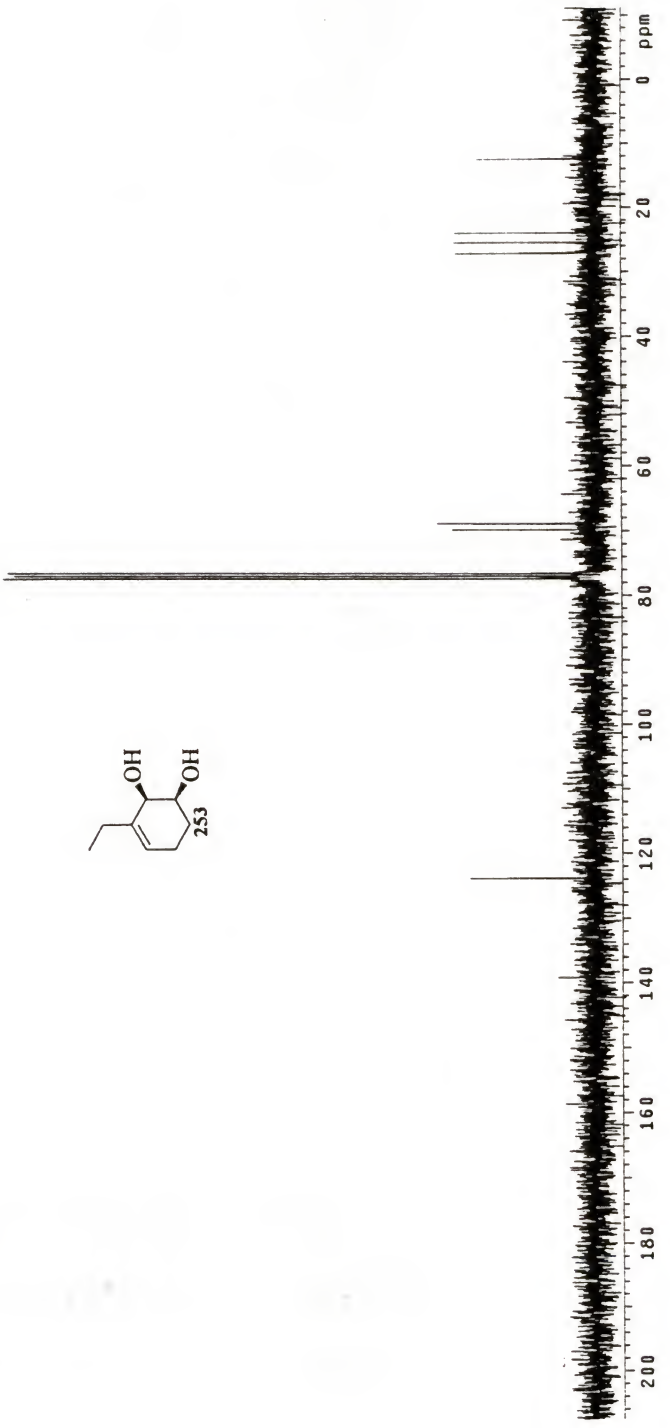

OH
OH
Br
255a
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
1.00
0.89
0.95
1.00
1.19
3.10
2.00
2.65
2.70

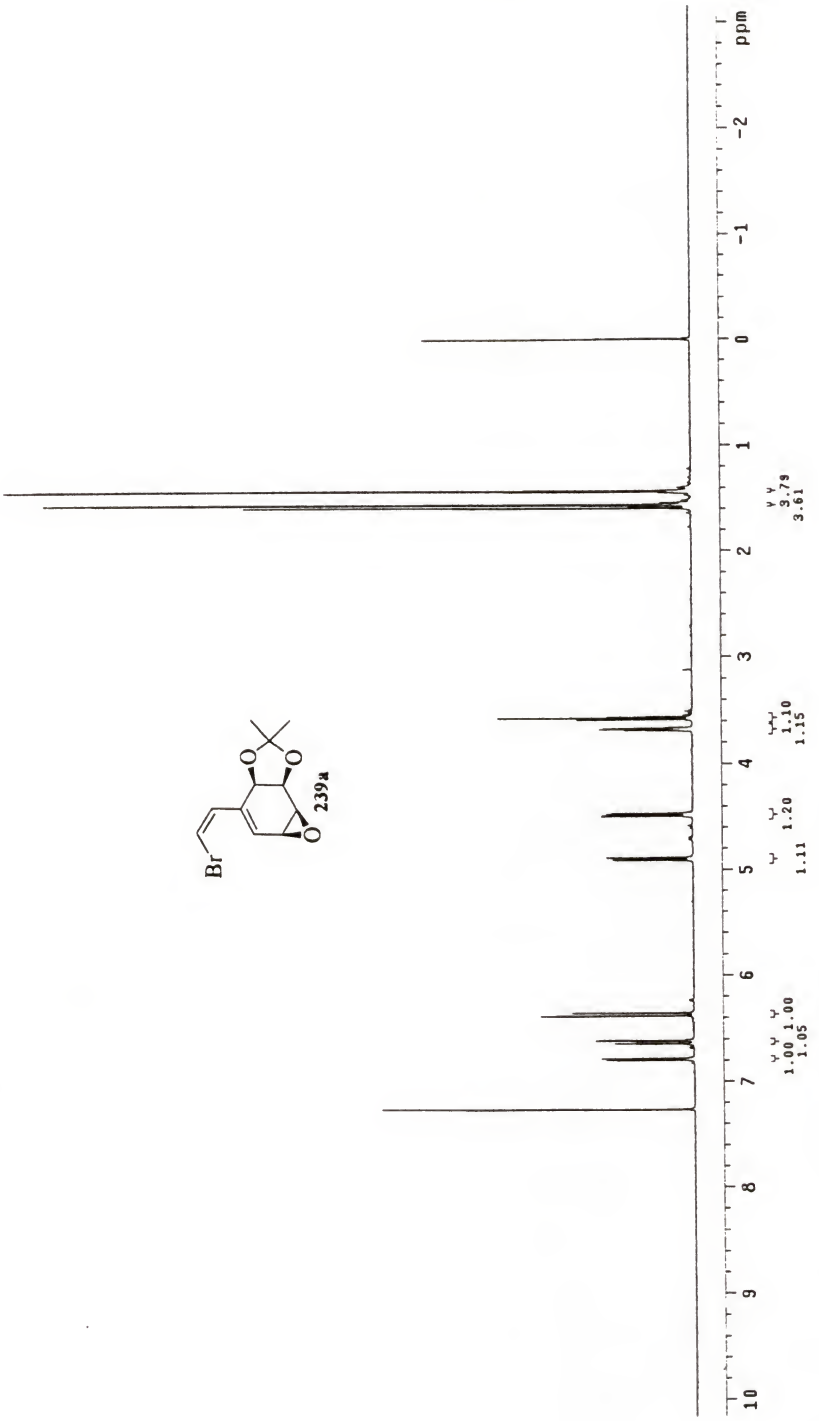

Br
OH
OH
255b
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
0.89
0.93
1.00
1.02
1.04
4.42
2.29
0.86

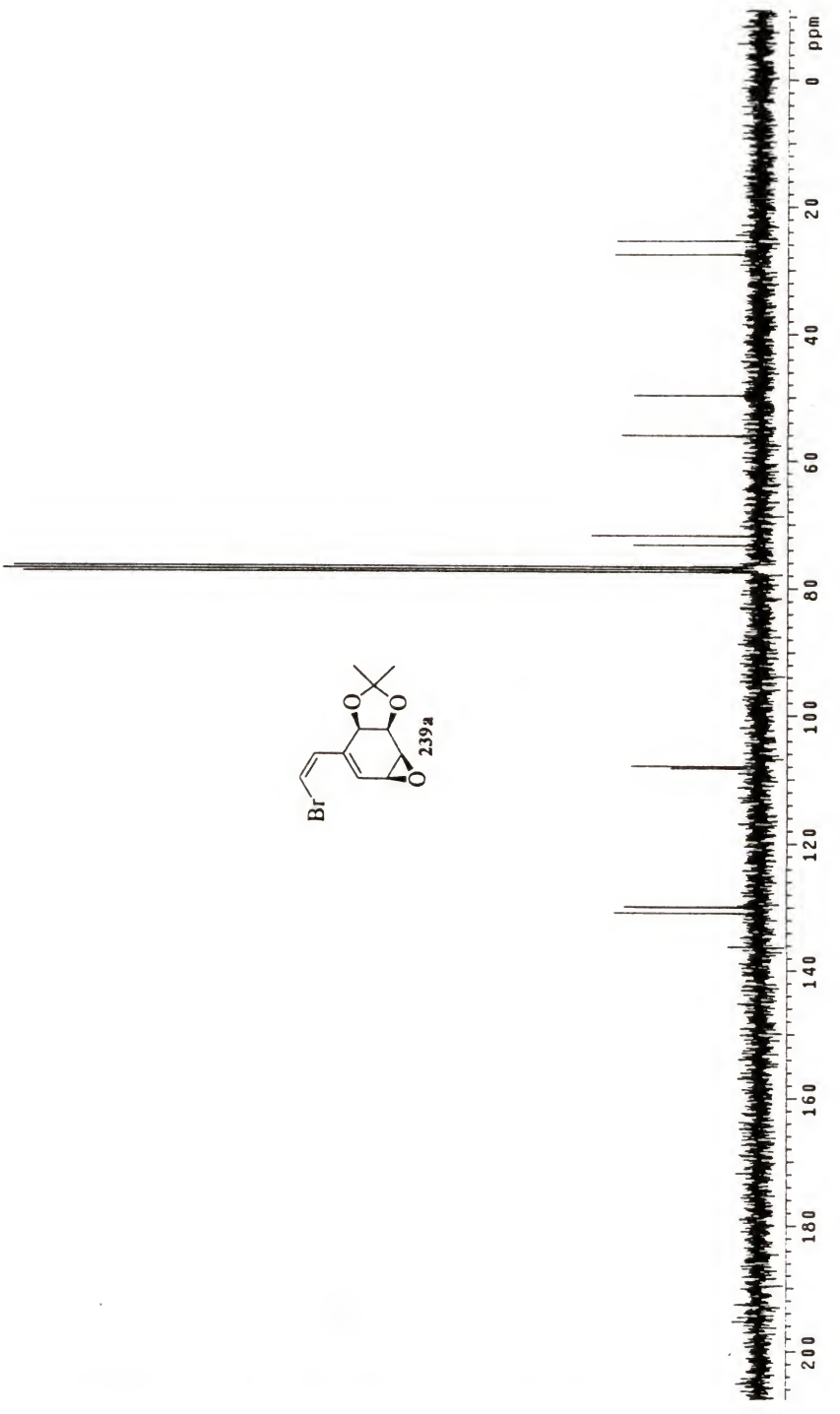

256
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
0.96 1.02
1.09 1.14
1.00 1.12
1.25 2.72
1.30 6.93

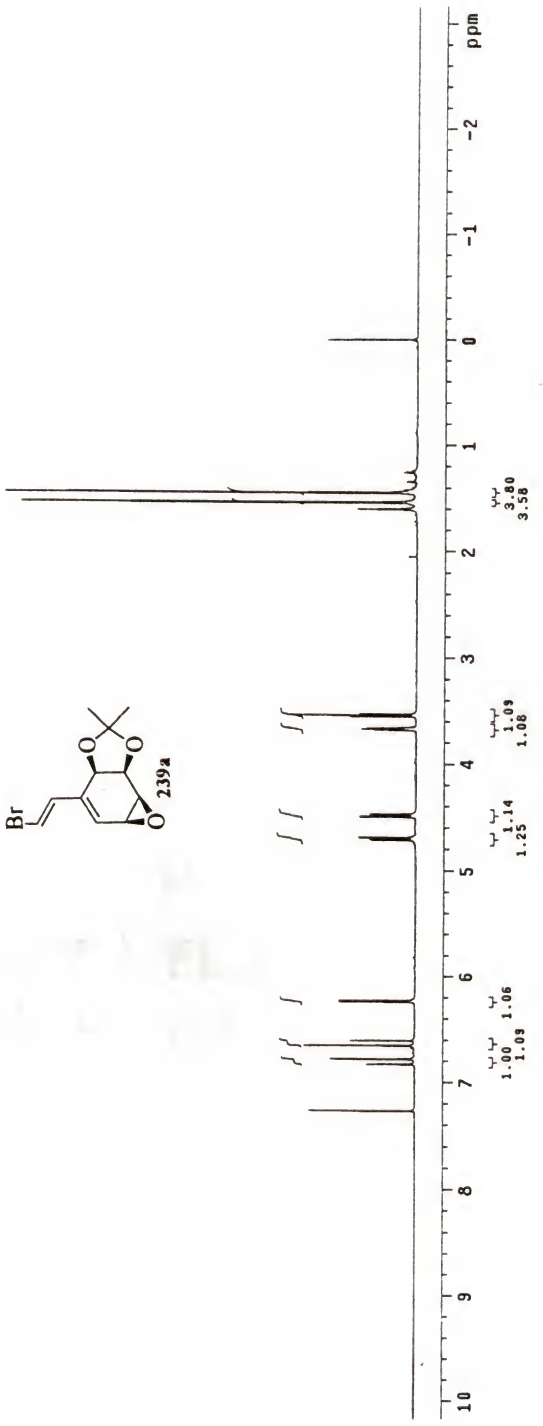

ppm
0
20
40
60
80
100
120
140
160
180
200
220
256

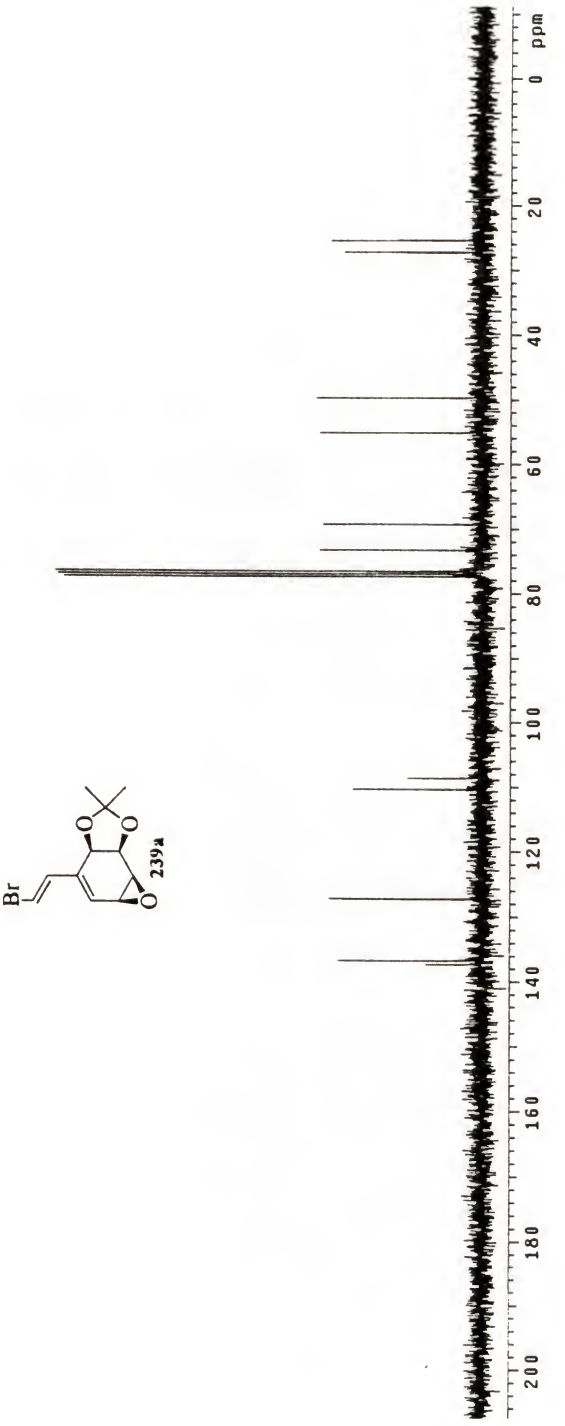

OH
OH
253
ppm
1.00
1.11
1.08
6.90
3.18
3.28

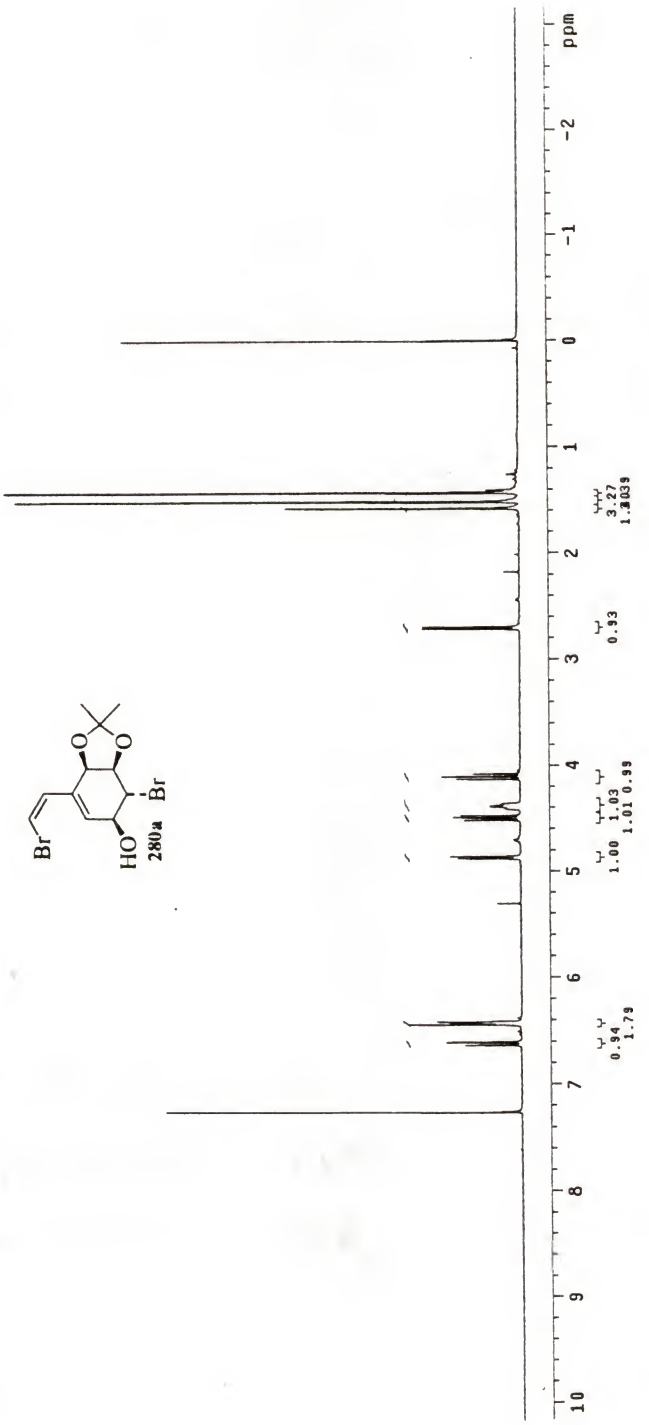

OH
OH
253
0
20
40
60
80
100
120
140
160
180
200
ppm

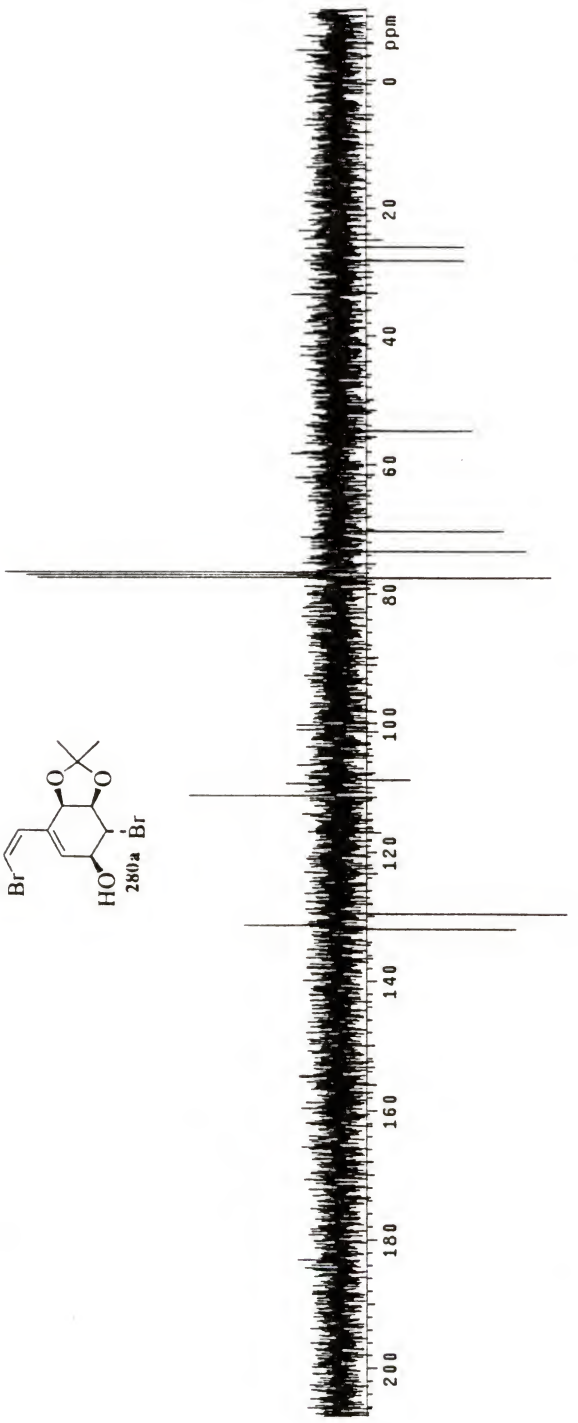

Br
O
O
O
239a
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
1.00 1.00
1.05
1.11
1.20
1.10
1.15
3.79
3.61

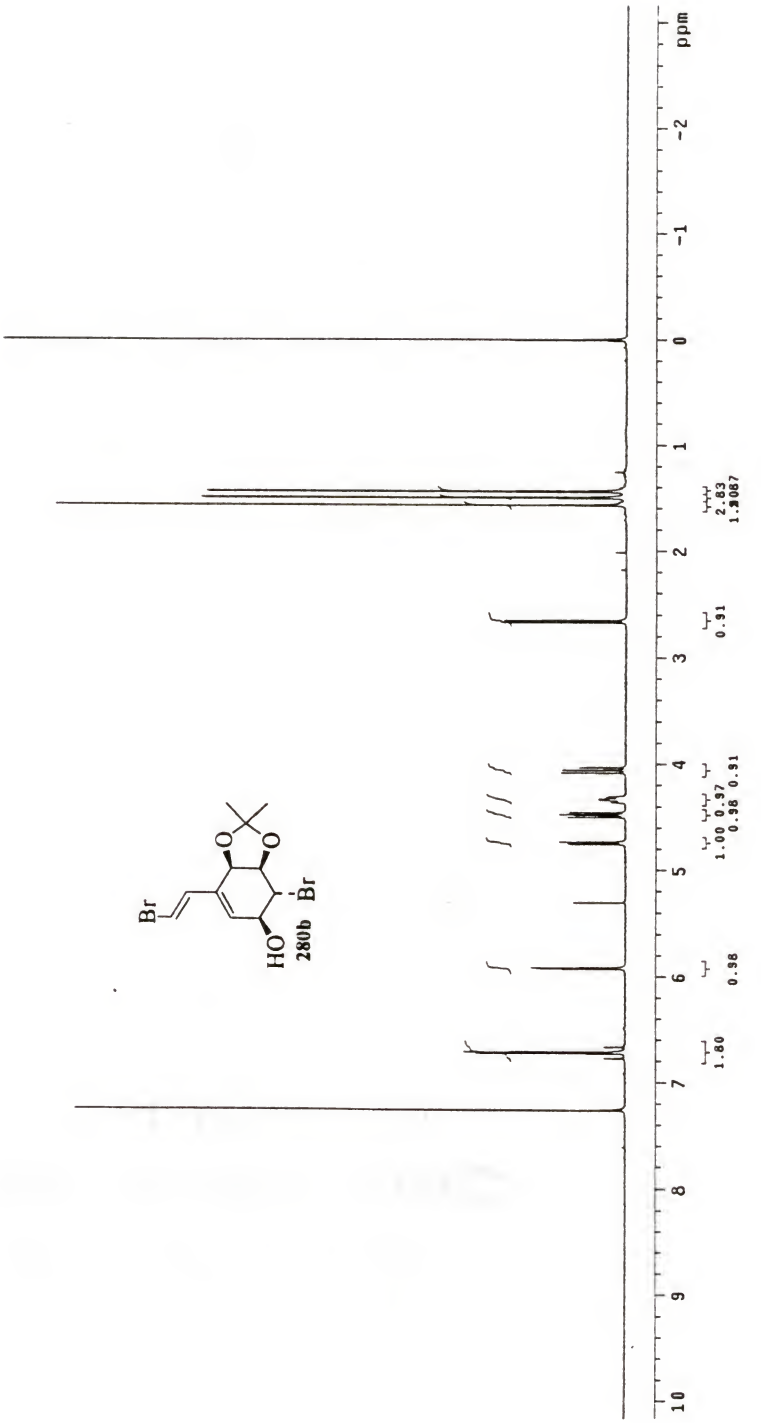

Br
239a
200
180
160
140
120
100
80
60
40
20
0
ppm

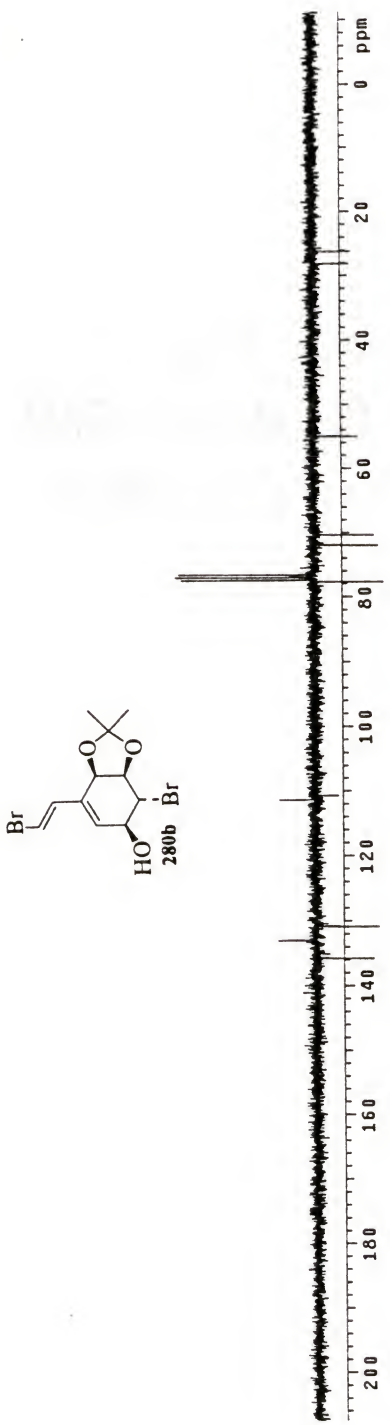

Br
O
O
O
239a
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
1.00
1.03
1.06
1.14
1.25
1.09
1.08
3.80
3.58

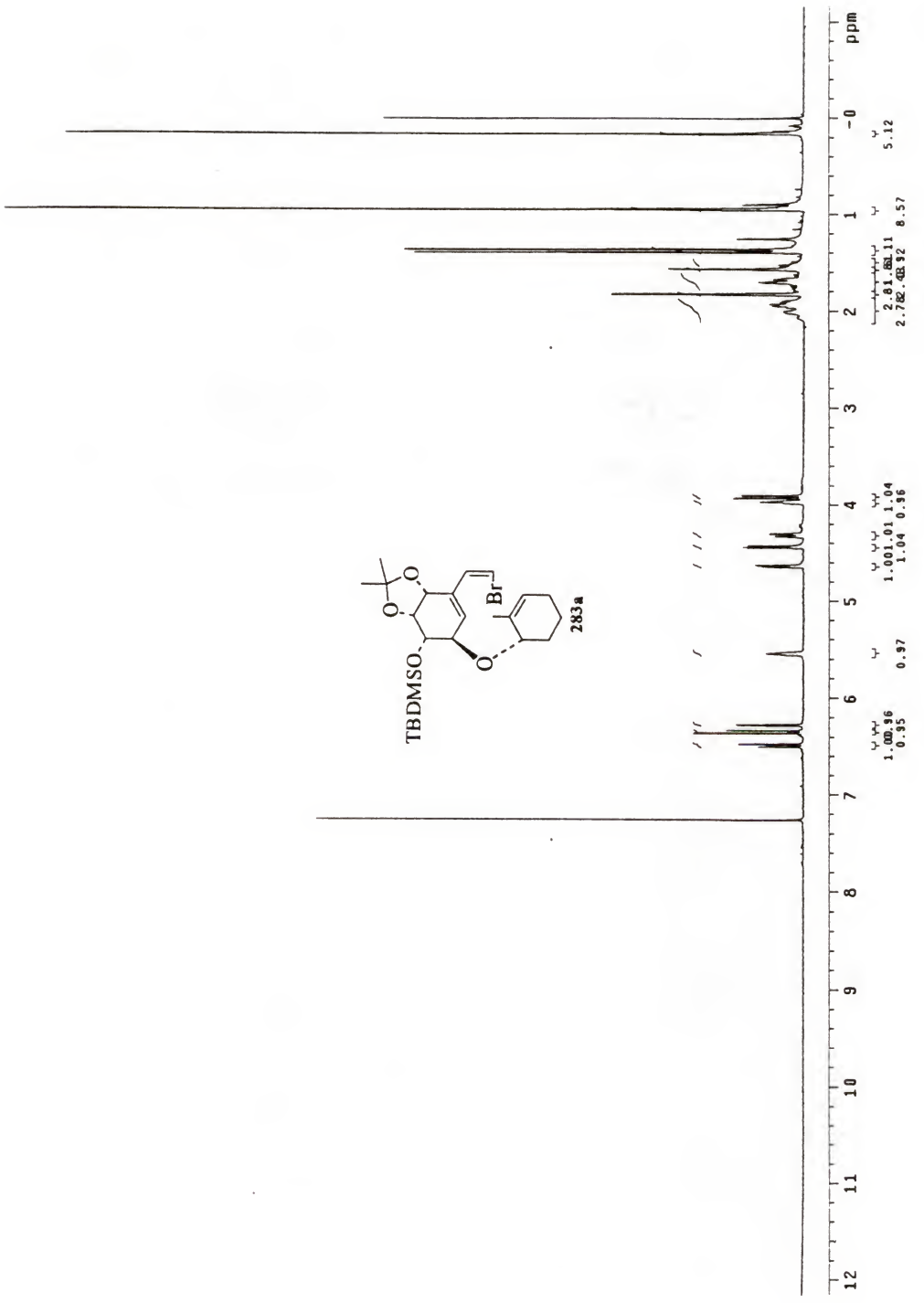

Br
O
O
O
239a
200
180
160
140
120
100
80
60
40
20
0
ppm

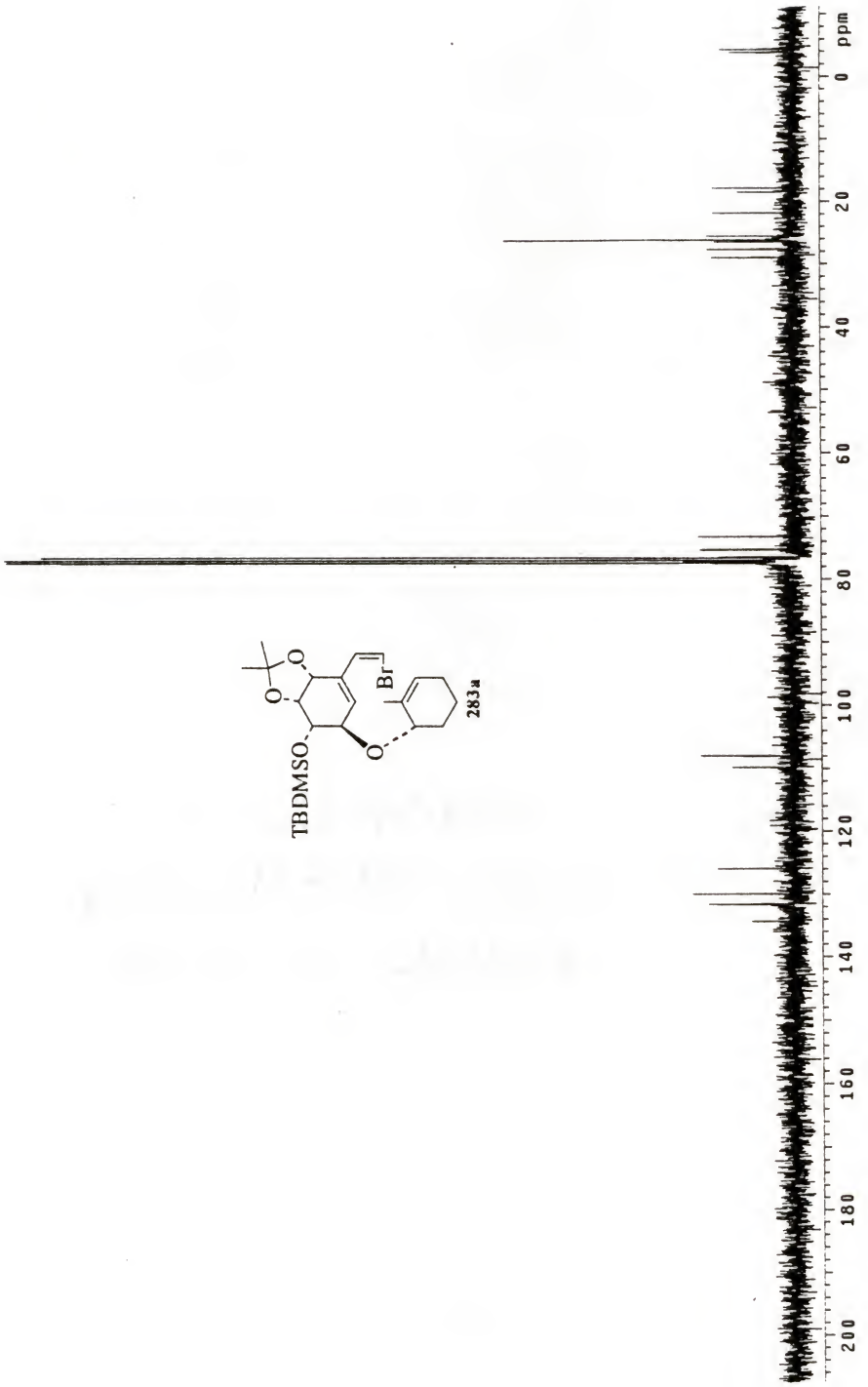

Br
HO
Br
280a
ppm

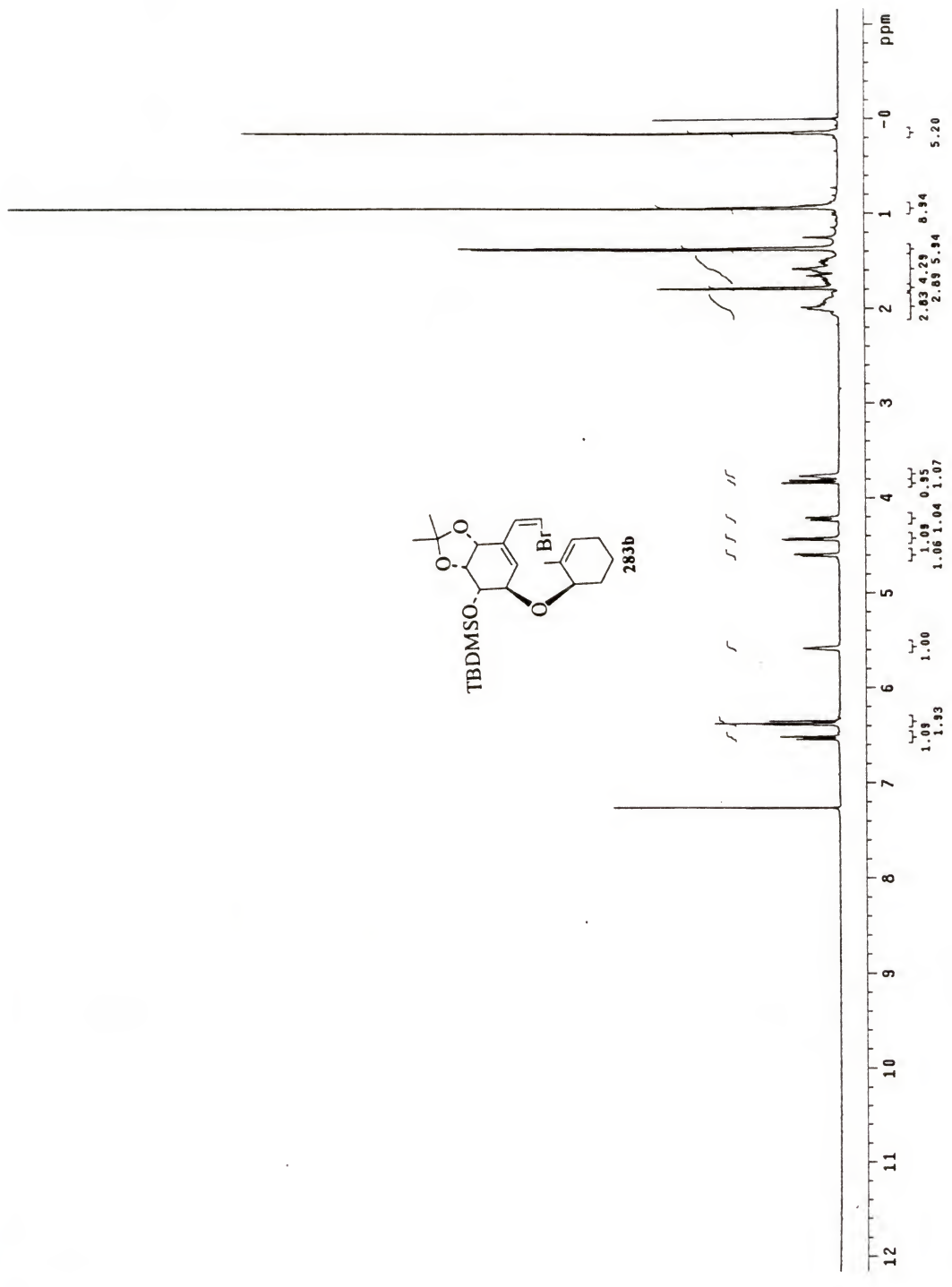

Br
HO
Br
280a
0 ppm
20
40
60
80
100
120
140
160
180
200

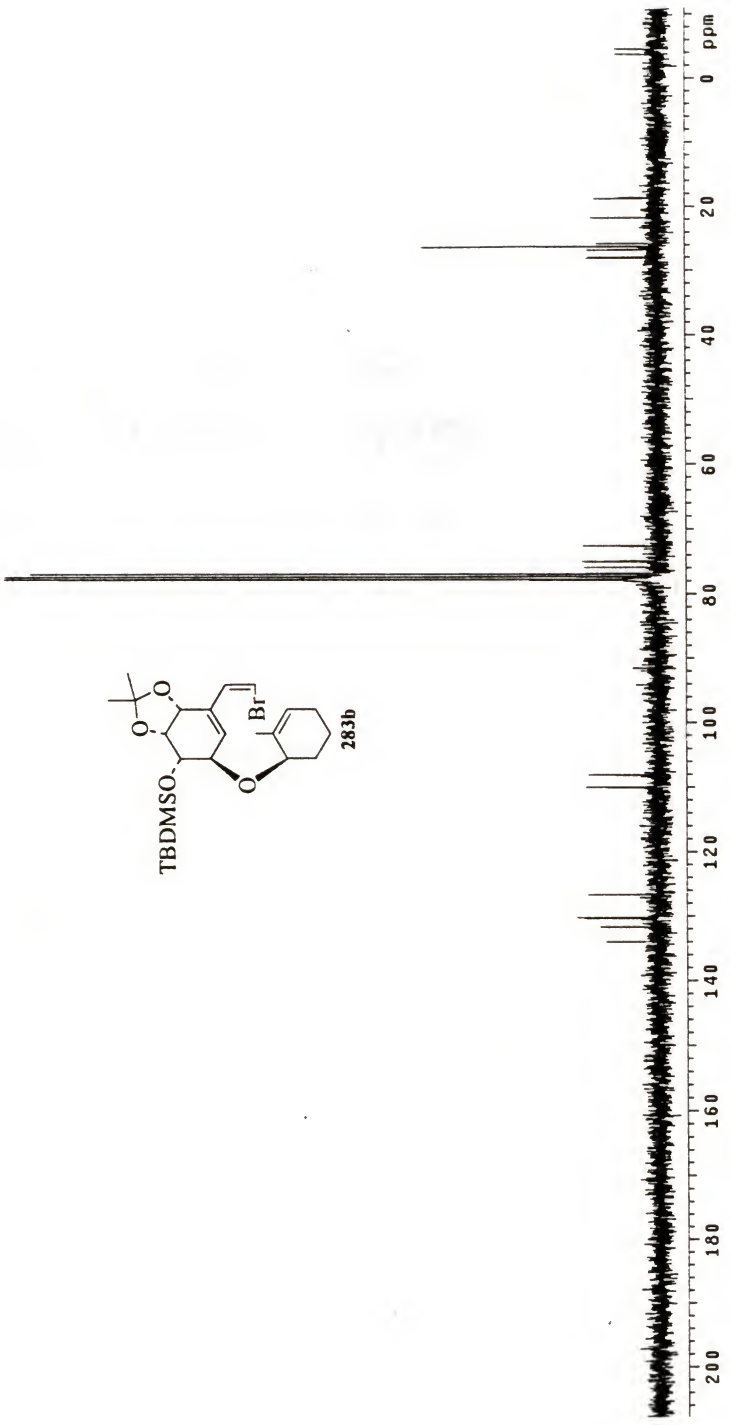

Br
HO
O
O
Br
280b
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
-2
1.60
0.98
1.00
0.97
0.98
0.91
0.91
2.83
1.9087

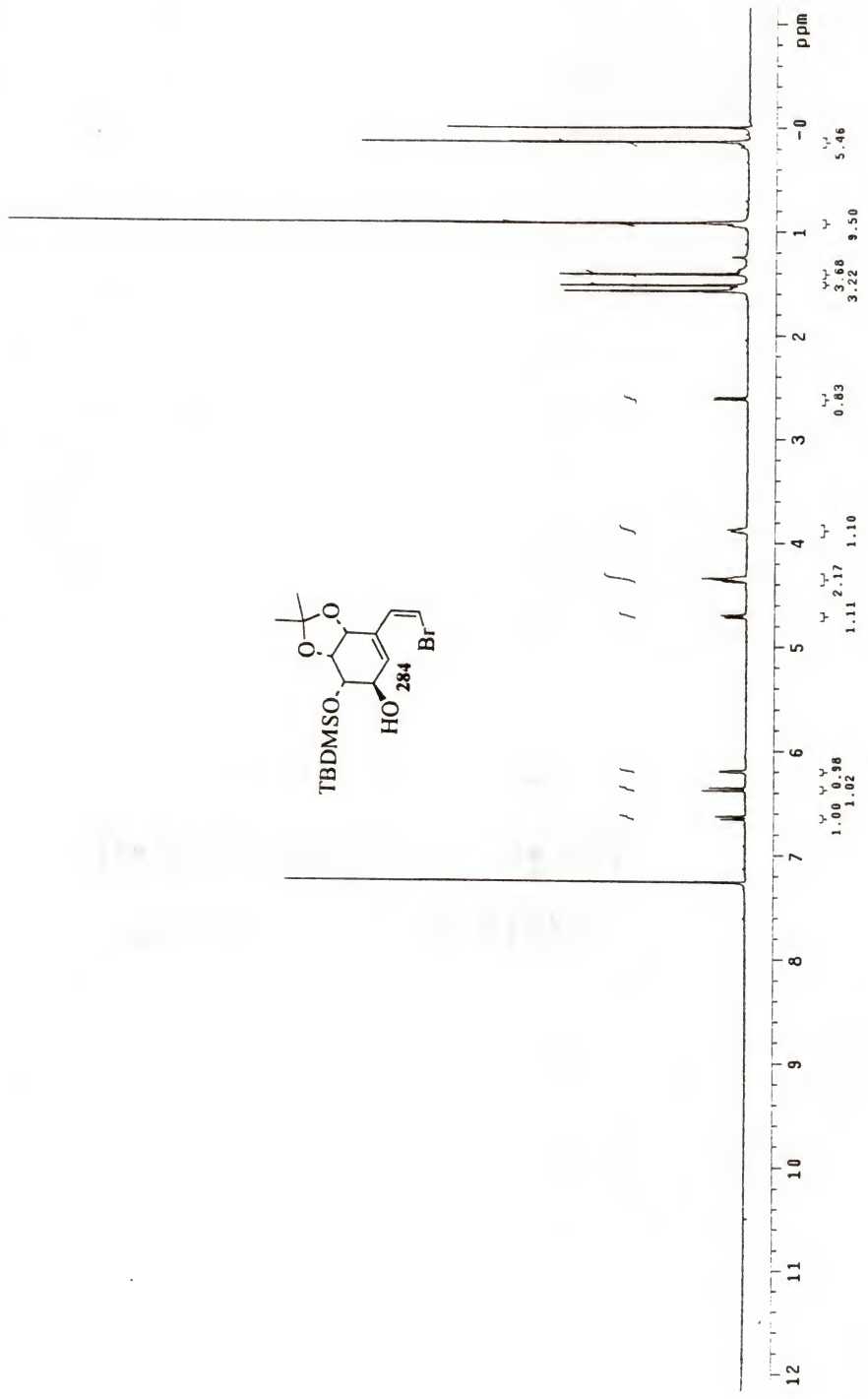

Br
HO
280b
Br
O
O
200
180
160
140
120
100
80
60
40
20
0 ppm


TBDMSO
Br
283a
ppm


TBDMSO
Br
283a
200
180
160
140
120
100
80
60
40
20
0
ppm


TBDMSO
Br
O
O
O
283b
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
1.09
1.93
1.00
1.08
1.06
1.04
0.95
1.07
2.83
4.29
2.83
5.34
8.34
5.20


TBDMSO
Br
283b
200
180
160
140
120
100
80
60
40
20
0
ppm


TBDMSO
HO
284
Br
ppm
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0.38
1.02
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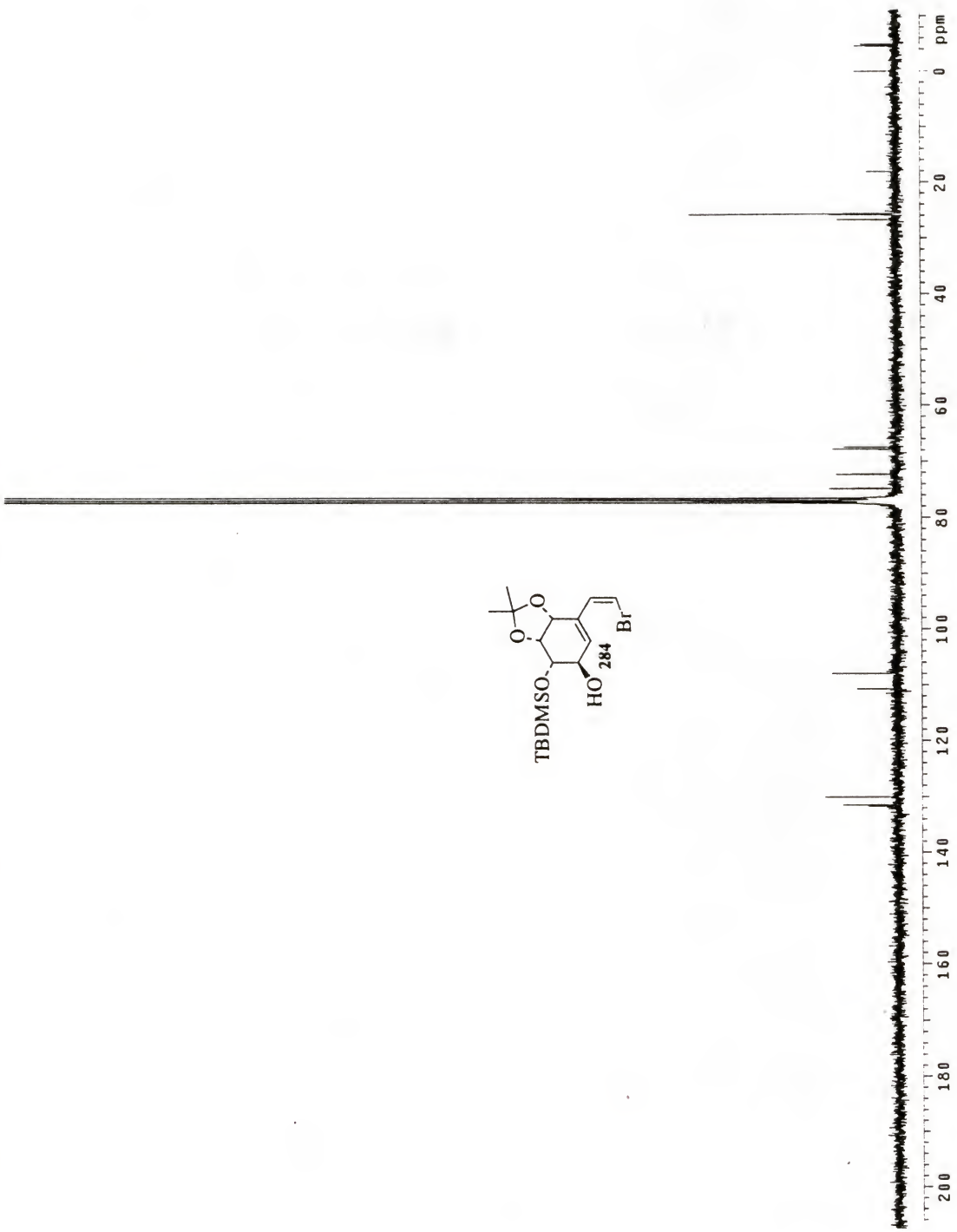
2.17
1.10
0.83
3.68
3.22
9.50
5.46


TBDMSO
HO
284
Br
200
180
160
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120
100
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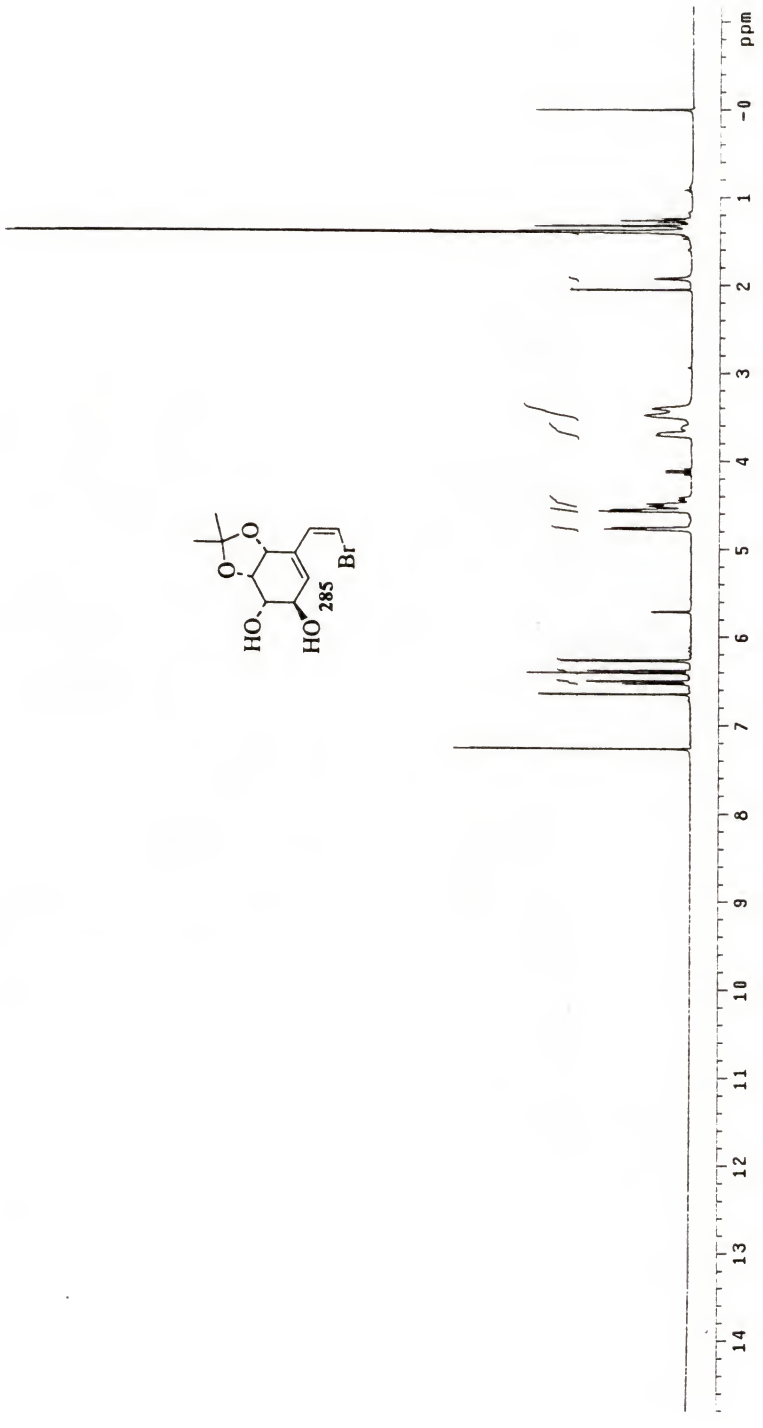
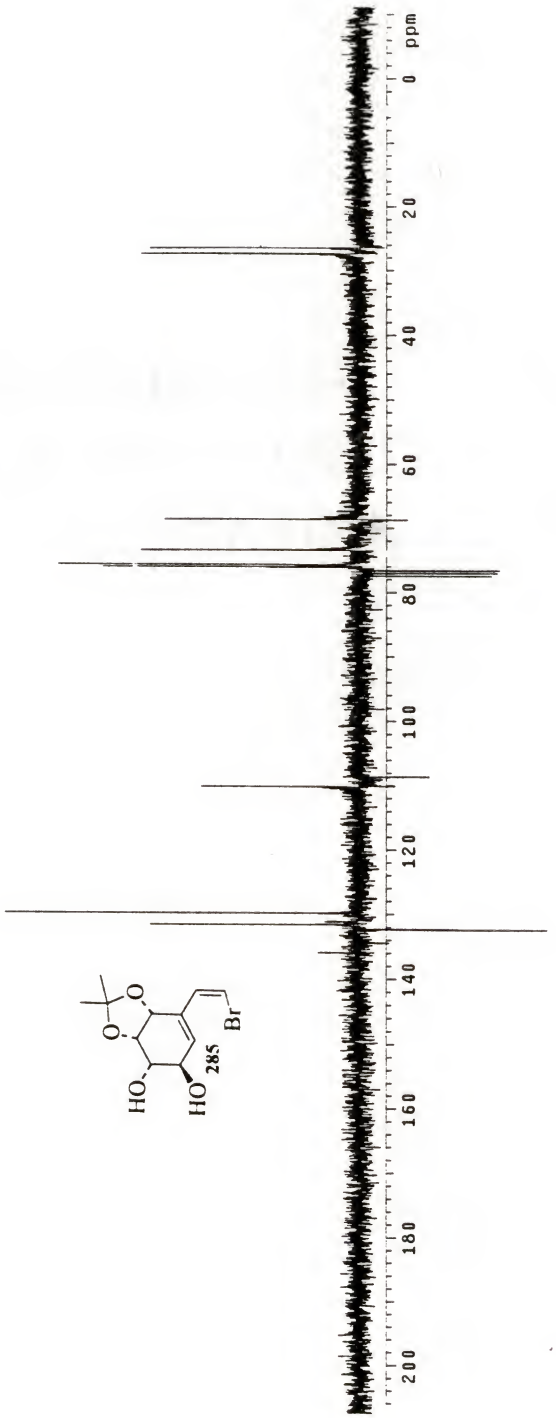
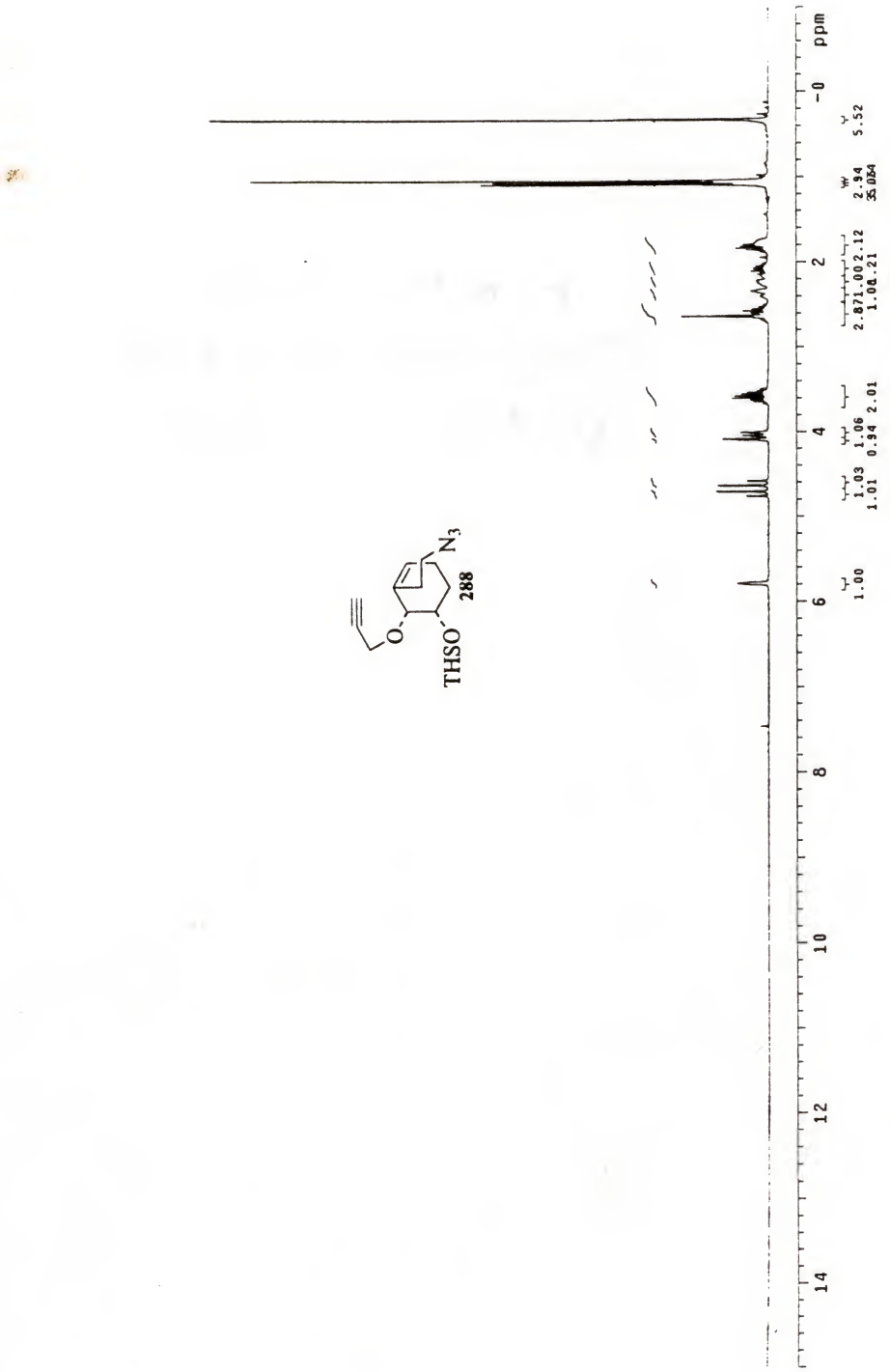
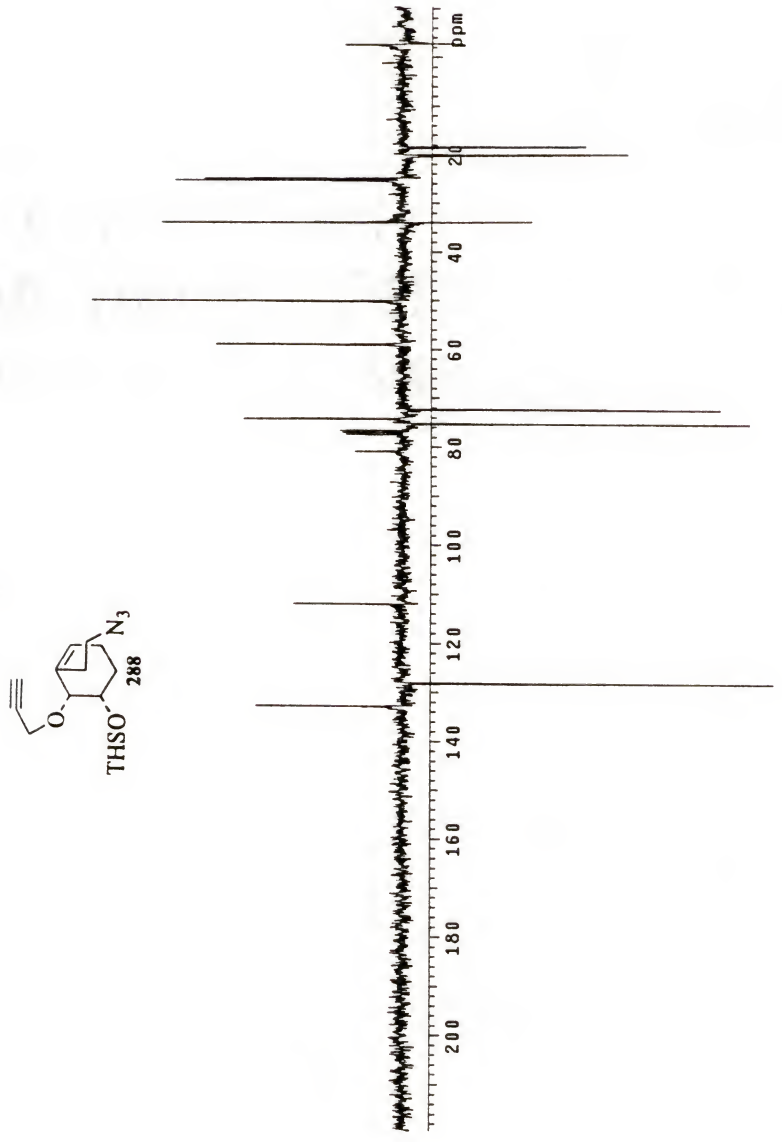
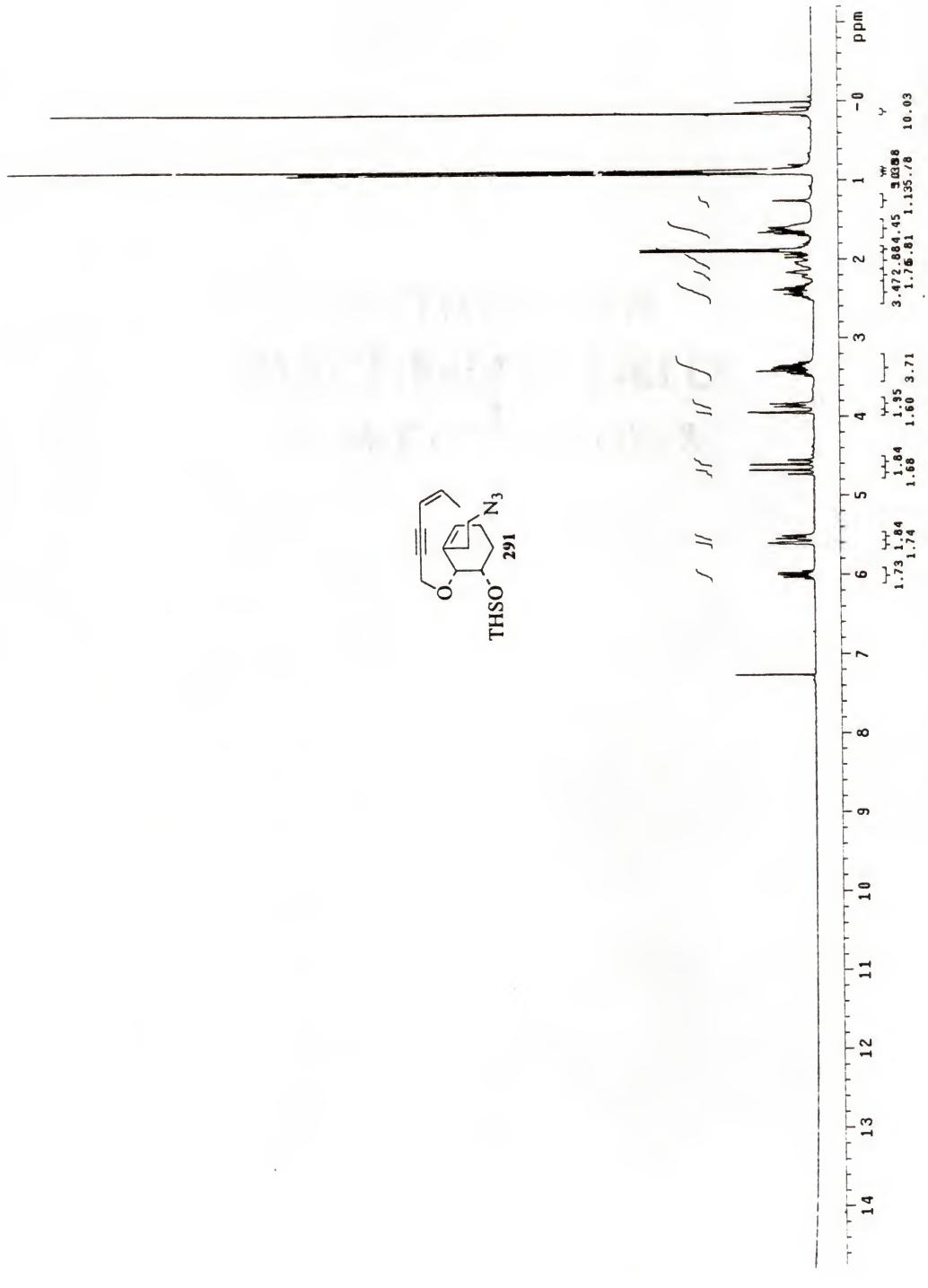
40
20
0
ppm

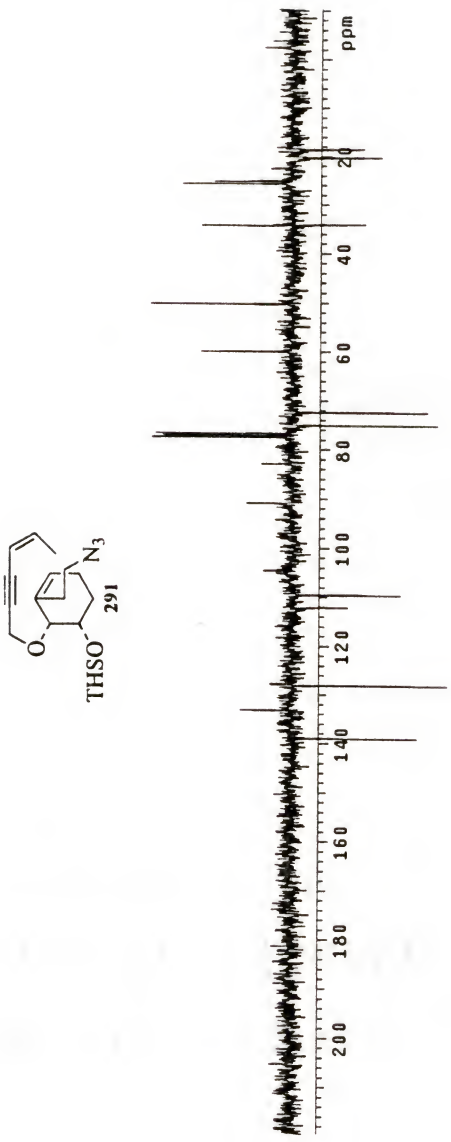

HO
HO
285
Br
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

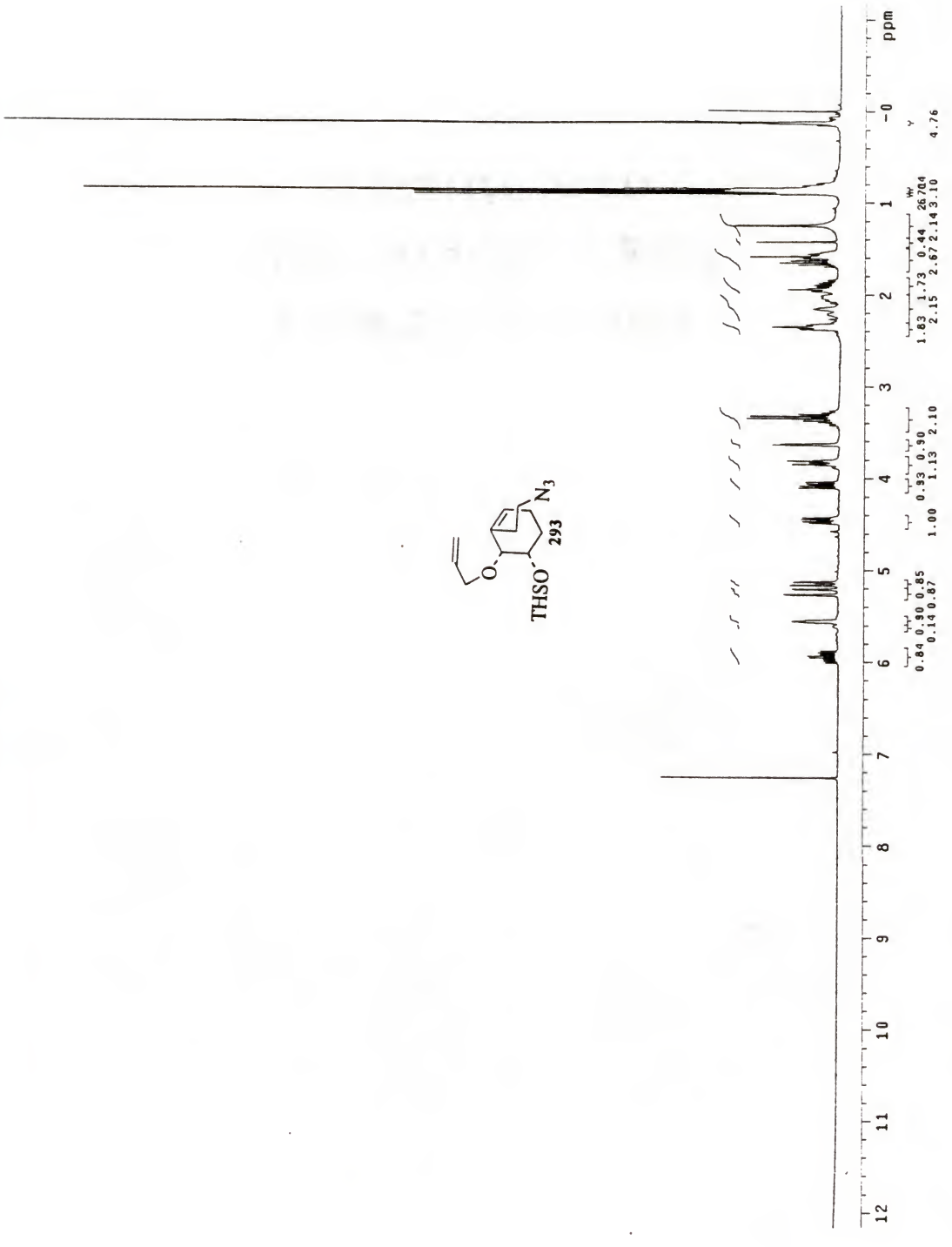

HO
HO
285
Br
O
O
O
200
180
160
140
120
100
80
60
40
20
0 ppm


THSO
288
N_3
O
ppm
1.00
1.03
1.01
1.06
0.94
2.01
2.871.00
2.12
1.08.21
2.94
35.054
5.52


ppm
20
40
60
80
100
120
140
160
180
200
O
THSO
288
N3


THSO
O
N3
291
ppm


N3
291
THSO
O
ppm
20
40
60
80
100
120
140
160
180
200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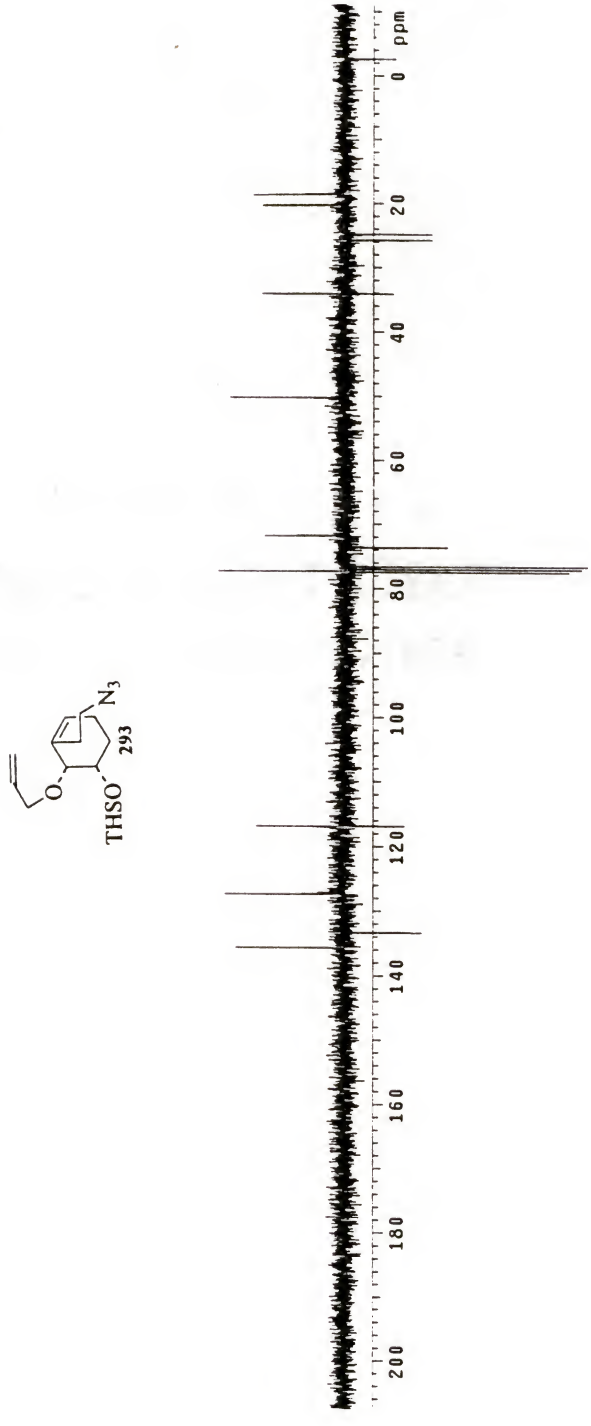
N_3
ppm


THSO
293
O
N3
ppm
0
20
40
60
80
100
120
140
160
180
200

REFERENCES

1. Deronse, J.F. *Ann. Chim.* **1803**, *45*, 257.

2. Deguin, M.A. *Ann. Chim.* **1806**, 225.

3. Serturner, F.W.A. *Trommdorff's J. Pharm.* **1806**, *14*, 47.

4. Gulland, J.M.; Robinson, R. *Proc. Mem. Manchester Lit. Phil. Soc.* **1925**, *69*, 79.

5. For a review on the elucidation of the morphine structure see: Butora, G.; Hudlicky, T. in: *Organic Synthesis: Theory & Applications.* Vol. 4, Hudlicky, T., Ed., JAI Press Inc., New York, 1998, p. 1-54.

6. a. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109; b. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1954**, *76*, 1380.

7. For a review on the total syntheses of morphine see: Hudlicky, T.; Butora, G.; Fearnley, S.P.; Gum, A.G.; Stabile, M. in: *Studies in Natural Products Chemistry*. Vol 18, Atta-ur-Rahman, Ed., Elsevier Science, Amsterdam, 1996, p. 43-107.

8. Rice, K.C. *J. Org. Chem.* **1980**, *45*, 3135.

9. Tius, M.A.; Kerr, M.A. *J. Am. Chem. Soc.* **1992**, *114*, 5959.

10. Elad, D.; Ginsburg, D. *J. Am. Chem. Soc.* **1954**, *76*, 312.

11. Barton, D.H.R.; Kirby, G.W.; Steglich, W.; Thomas, G.M. *Proc. Chem. Soc.* **1963**, 203.

12. a. Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550; b. Grewe, R.; Fischer, H.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1; c. Grewe, R.; Fischer, H. *Chem. Ber.* **1963**, *96*, 1520.

13. Morrison, G.C.; Waite, R.O.; Shavel, Jr. J. *Tetrahedron Lett.* **1967**, 4055.

14. Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. (C),* **1969**, 2030.

15. a. Schwartz, M.A.; Mami, I.S. *J. Am. Chem. Soc.* **1975**, *97*, 1239; b. Schwartz, M.A.; Pham, P.T.K. *J. Org. Chem.* **1988**, *53*, 2318.

16. Lie, T.S.; Maat, L.; Beyerman, H.C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 419.

17. Evans, D.A.; Mitch, C.H. *Tetrahedron Lett.* **1982**, *23*, 285.

18. Moos, W.H.; Gless, R.D.; Rapoport, H. *J. Org. Chem.* **1993**, *48*, 227.

19. White, J.D.; Caravatti, T.B.; Kline, T.B.; Edstrom, E.; Rice, K.C.; Brossi, A. *Tetrahedron* **1983**, *39*, 2393.

20. Ludwig, W.; Schafer, H.J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1025.

21. Toth, J.E.; Fuchs, P.L. *J. Org. Chem.* **1987**, *52*, 473; Toth, J.E.; Hamann, P.R.; Fuchs, P.L. *J. Org. Chem.* **1988**, *53*, 4694.

22. a. Parker, K.A.; Fokas, D. *J. Am. Chem. Soc.* 1992, *114*, 9688; b. Parker, K.A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3927; c. Parker, K.A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933.

23. Hong, C.Y.; Kado, N.; Overman, L.E. *J. Am. Chem. Soc.* **1993**, *115*, 11028

24. Parsons, P.J.; Penkett, C.S.; Shell, A.J. *Chem. Rev.* **1996**, *96*, 195.

25. Mulzer, J.; Durner, G.; Trauner, D. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2830.

26. a. White, J.D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250; b. White, J.D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.

27. Trauner, D.; Bats, J.W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908.

28. Diels, O.; Alder, K. *Justus Liebigs Ann. Chim.* **1928**, *460*, 98.

29. Woodward, R.B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

30. Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry Part A: Structure and Mechanism* 3rd Ed., Plenum Press, New York, 1990, p. 632.

31. Alder, K.; Schumacher, M. *Fortschr. Chem. Org. Naturst.* **1953**, *10*, 66.

32. House, H.O., Cronin, T. *J. Org. Chem.* **1965**, *30*, 1061.

33. Boeckman, R.K. Jr.; Ko, S.S. *J. Am. Chem. Soc.* **1980**, *102*, 7146; Boeckman, R.K. Jr.; Ko, S.S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.

34. Roush, W.R. *J. Org. Chem.* **1979**, *44*, 4008.

35. Roush, W.R.; Gillis, H.R.; Ko, A.I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

36. Bajorek, J.J.S.; Sutherland, J.K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1559.

37. Jung, M.E.; Halweg, K.M. *Tetrahedron Lett.* **1981**, *22*, 3932.

38. Wu, T-C.; Houk, K.N. *Tetrahedron Lett.* **1985**, *26*, 2293.

39. Brown, F.K.; Houk, K.N. *Tetrahedron Lett.* **1985**, *26*, 2297.

40. Brasca, M.G.; Broughton, H.B.; Craig, D.; Ley, S.V.; Somovilla, A.A.; Toogood, P.L. *Tetrahedron Lett.* **1988**, 1853.

41. Ihara, M.; Kawaguchi, A.; Ueda, H.; Chihiro, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1331.

42. Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

43. Lutz, E.F.; Bailey, G.M. *J. Am. Chem. Soc.* **1964**, *86*, 3899.

44. Trost, B.M.; Ippen, J.; Vladuchick, W.C. *J. Am. Chem. Soc.* **1977**, *99*, 8116.

45. Bartlett, A.J.; Laird, T.; Ollis, W.D. *J. Chem. Soc., Chem. Commun.* **1974**, 496.

46. Gassman, P.G.; Singleton, D.A. *J. Am. Chem. Soc.* **1984**, *106*, 6085.

47. Wender, P.A.; Jenkins, T.E. *J. Am. Chem. Soc.* **1989**, *111*, 6432.

48. Jolly, R.S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965.

49. Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

50. Van Royen, L.A.; Mijingheer, R.; De Clercq, P.J. *Tetrahedron Lett.* **1985**, *26*, 4667.

51. Dauben, W.G.; Krabbenhoft, H.O. *J. Am. Chem. Soc.* **1976**, *98*, 1992.

52. Keay, B.A.; Dibble, P.W. *Tetrahedron Lett.* **1989**, *30*, 1045.

53. Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

54. Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

55. Burke, S.D.; Strickland, S.M.S.; Powner, T.H. *J. Org. Chem.* **1983**, *48*, 454.

56. Funk, R.L.; Zeller, W.E. *J. Org. Chem.* **1982**, *47*, 180.

57. Ciganeck, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.

58. Boger, D.L.; Patel, M.; Mullican, M.D. *Tetrahedron Lett.* **1982**, *23*, 4559.

59. Handa, S.; Jones, K.; Newton, C.G.; Williams, D.J. *J. Chem. Soc., Chem. Commun.* **1985**, 1362.

60. Kametani, T.; Suzuki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1373.

61. Constanzo, M.J. Ph.D. Dissertation presented to Temple University, 1988.

62. Wu, C. Ph.D. Dissertation presented to Columbia University, 1990.

63. Hudlicky, T.; Boros, C.H.; Boros, E.E. *Synthesis* **1992**, 174.

64. Hudlicky, T.; Butora, G.; Fearnley, S.P.; Gum, A.G.; Persichini III, P.J.; Stabile, M.R.; Merola, J.S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2393.

65. Carlini, R.; Higgs, K.; Rodrigo, R.; Taylor, N. *J. Chem. Soc., Chem. Commun.* **1998**, 65.

66. a. Butora, G.; Gum, A.G.; Hudlicky, T.; Abboud, K.A. *Synthesis* **1998**, 275; b. Gum, A.G. Ph.D. dissertation presented to the University of Florida, 1996.

67. Grovenstein Jr., E.; Lee, D.E. *J. Am. Chem. Soc.* **1953**, *75*, 2639.

68. Wolinsky, J.; Erickson, K.L. *J. Org. Chem.* **1965**, *30*, 2208.

69. Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.

70. Ramirez, F.; Desai, N.B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

71. Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemistsu, O.; Tsuji, J. *Tetrahedron Lett.* **1996**, *37*, 6759.

72. Petasis, N.A.; Zavialov, I.A. *Tetrahedron Lett.* **1996**, *37*, 567.

73. a. Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* **1968**, *7*, 3795; b. Gibson, D.T.; Hensley, M; Yoshioka, H.; Mabry, T.J. *Biochemistry* **1970**, *9*, 1626.

74. Motherwell, W.B.; Williams, A.S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2031.

75. The fermentations were carried out in a 12-L fermentor using IPTG as the inducer. Hudlicky, T.; Stabile, M.R.; Gibson, D.T.; Whited, G.M. *Org. Synth.* **1999**, *76*, 77.

76. Boyd, D.R.; Sharma, N.D.; Byrne, B.; Hand, M.V.; Malone, J.F.; Sheldrake, G.N.; Blacker, J.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935.

77. Stabile, M.R.; Hudlicky, T.; Meisels, M.L. *Tetrahedron: Asymmetry* **1995**, *6*, 537.

78. Hudlicky, T.; Endoma, M.A.A.; Butora, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2187.

79. Novak, B.H.; Hudlicky, T. *Tetrahedron: Asymmetry* **1999**, *10*, 2067.

80. Hudlicky, T.; Boros, C.H. *Tetrahedron Lett.* **1993**, *34*, 2557.

81. Nguyen, B.V.; York, C.; Hudlicky, T. *Tetrahedron* **1997**, *53*, 8807.

82. Adam, G.; Seebach, D. *Synthesis* **1988**, 373.

83. Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.

84. Rosen, T.; Lico, I.; Chu, D. *J. Org. Chem.* **1988**, *53*, 1581.

85. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

86. Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786.

87. Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L.D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.

88. Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

89. Kasatkin, A.; Whitby, R.J. *J. Am. Chem. Soc.* **1999**, *121*, 7039.

90. Negishi, E-i; Takahashi, T.; Baba, S.; Van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2401.

91. Zweifel, G.; Steele, R.B. *J. Am. Chem. Soc.* **1967**, *89*, 5085.

92. Kappe, C.O.; Murphree, S.S.; Padwa, A. *Tetrahedron* **1997**, *42*, 14179.

93. a. Zanetti, J.E. *J. Am. Chem. Soc.* **1927**, *49*, 1065; b. Zanetti, J.E.; Bashour, J.T. *J. Am. Chem. Soc.* **1939**, *61*, 2249.

94. Harrington, P.J.; Hegedus, L.S. *J. Org. Chem.* **1984**, *49*, 2657.

95. Yokoyama, Y.; Takahashi, M.; Kohno, Y.; Kataoko, K.; Fujikawa, Y.; Murakami, Y. *Heterocycles* **1990**, *31*, 803.

96. For a review on silicon-tethered reactions see: Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.

97. a. Craig, D.; Reader, J.C. *Tetrahedron Lett.* **1990**, *31*, 6585; b. Craig, D.; Reader, J.C. *Tetrahedron Lett.* **1992**, *33*, 4073; c. Craig, D.; Reader, J.C. *Tetrahedron Lett.* **1992**, *33*, 6165.

BIOGRAPHICAL SKETCH

Bennett Haines Novak was born in Urbana, IL on August 25, 1970. He grew up in southeast Illinois, attending East Richland High School in Olney, IL, and Washington Senior High School in Washington, MO. He moved back to Illinois in 1989 and finished his Associate of Arts and Sciences degree at Richland Community College in Decatur, IL. He then transferred to Illinois State University to major in biology but became more interested in chemistry. After completing a year of organic chemistry he joined the research group of Professor John F. Hansen and worked on pyrazole chemistry. After finishing his bachelor of science degree he decided to stay at Illinois State University and pursue a master's degree under the direction of Professor Timothy D. Lash. His thesis research concentrated on the synthesis of porphyrins with extended aromatic systems. Before moving on to his Ph.D. school he did a brief internship at Eastman Kodak in Rochester, NY. While there he worked under the direction of Dr. Steve Evans in one of the dye labs. Currently, he is working toward his Ph.D. in chemistry under the direction of Professor Tomas Hudlicky. His major area of focus involves the synthesis of morphinan skeletons using both basic synthetic organic chemistry methods as well as basic microbiology methods. After graduate school he plans to do post-doctoral research in the Department of Chemistry at the University of Arizona under the direction of Professor Robin Polt.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier, Jr.
Professor of Chemistry

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Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May 2000

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Dean, Graduate School